Appointment

From: Keigwin, Richard [Keigwin.Richard@epa.gov]
Sent: 9/26/2017 4:00:50 PM
To: Keigwin, Richard [Keigwin.Richard@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Miller, Wynne [Miller.Wynne@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; JILL.HOLIHAN@fmc.com; John.Cummings@fmc.com; Hughes, Hayley [hughes.hayley@epa.gov]
CC: Arnold, Elyssa [Arnold.Elyssa@epa.gov]; Anderson, Brian [Anderson.Brian@epa.gov]; Costello, Kevin [Costello.Kevin@epa.gov]; Britton, Cathryn [Britton.Cathryn@epa.gov]; Waleko, Garland [Waleko.Garland@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]

Subject: Pyrethroid Registration Review Status and Next Steps
Attachments: Pyrethroids presentation for ActingAA_100317 to Shannon.pptx
Location: Potomac Yard South - 12621

Start: 11/14/2017 3:00:00 PM
End: 11/14/2017 4:00:00 PM
Show Time As: Tentative

11/14: Slides from this morning attached.

John Cummings RE: Meeting purpose - The object of the discussion is to review the status of the pyrethroid Registration Review cases including timelines and next steps. I don't think there is the need for a formal agenda.

Logistics email thread:

Thank you Shannon. That date and time would work well.

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John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: Jewell, Shannon [mailto:jewell.shannon@epa.gov]
Sent: Tuesday, September 26, 2017 11:25 AM
To: John Cummings; Jill Holihan
Cc: Keigwin, Richard
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Hello John and Jill,

The November 14th date would be best on this end, as Rick's calendar is incredibly full for the month of October. Would 10am on the 14th work for you? If so, I will go ahead and schedule it on Rick's calendar.

Thank you for your understanding!

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Subject: RE: Tuesday's Pyrethroid Discussion

Rick (and Shannon),

The following dates would work for Jill and I to hold the postponed discussion on pyrethroid registration review with you and your team. Please let us know if any of the dates would work for you and your team.

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October 11
October 18
October 30
November 14

Thanks

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My apologies for the late notice.
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Pyrethroid Registration Review Status

November 14, 2017

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- Council for Advancement of Pyrethroid Human Risk Assessment (CAPHRA)
  - History, timeline, and research status
- Implication of CAPHRA research on regulatory decision-making
- Current versus potential status of pyrethroid human health risk
- Timing Uncertainties
- Ecological Risk Assessment Status
- Options/next steps

Exploration of Juvenile Sensitivity to Pyrethroids

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appropriateness of the ASR technique as a measure of pyrethroid induced toxicity, including suggestions to assure quality of the study design and resulting data
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Not an exhaustive list of all meetings or phone calls, but highlights the regularity of our check-ins with CAPHRA on their research program and status. In addition to status updates with a few individuals from PRD and HED, there were a number of technical updates for HED, as well as PMRA and DPR, and mgmt. updates for DDs and an a couple of occasions with the OD.

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Neurolemma	6/12	1/15	4/16	Report submitted 10/17; raw data needed for statistical validation, not yet submitted
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PBPK Code	12/12	Mid-2015	4/16	Code for SAP submitted 3/17; acknowledgement submission is not final code 8/17; final code not yet submitted
Part 3 – Model parameterization (5 additional pyrethroids)				
Chemical-specific Parameterization	12/13	TBD	9/16	"Acknowledgement of evolving parameter database" in 9/6/17 email, 3/18?

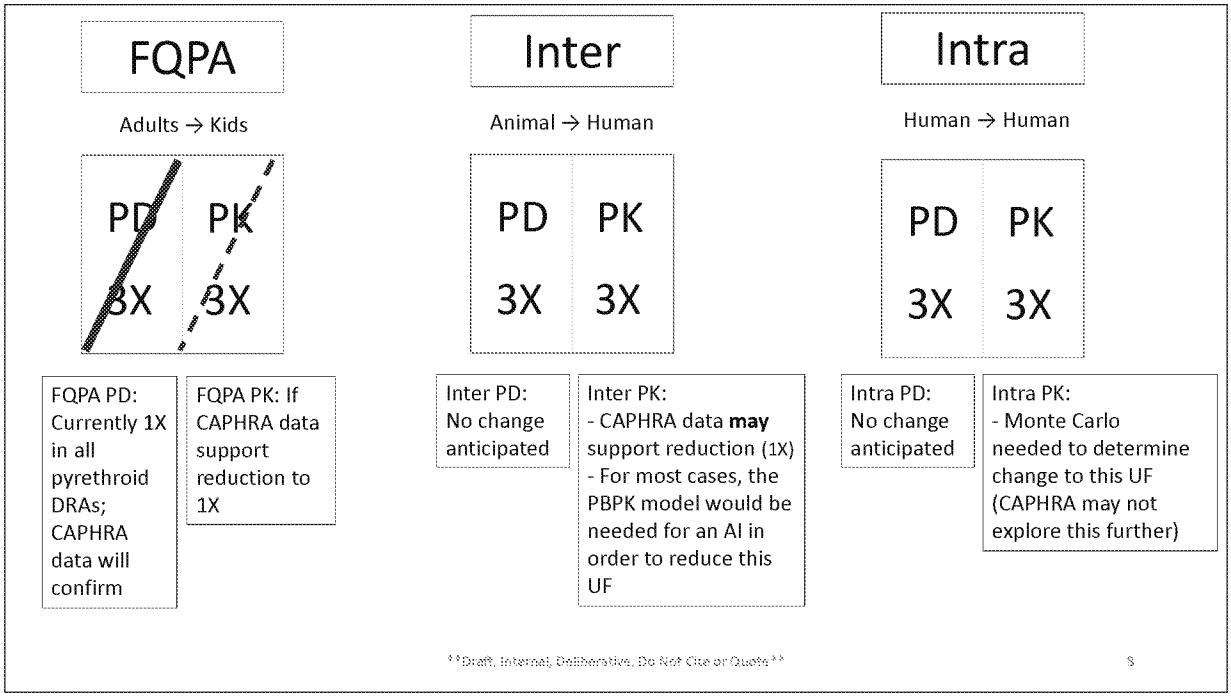
There are a number of milestones involved in CAPHRA's research program, but I wanted to highlight a few of the items, like the acute startle and neurolemma work, which have been the topic of many discussions over the years, and their shifting timeframes.

Looking at the right-hand column "current status," there are still some outstanding items including data needed for statistical validation of the neurolemma work, the final PBPK code for permethrin and deltamethrin, and the chemical-specific data needed to parameterize the model for the additional 5 pyrethroids.

Potential Impact of CAPHRA Data

- POD likely to change for chemicals with PBPK models
- FQPA safety factor may change for the class
- Interspecies factor may change for chemicals with PBPK models

Before moving forward, we just wanted to highlight the potential impact of the CAPHRA data as is currently understood.



FQPA – Neurolemma and acoustic startle will be important in confirming removal of 3X PD; and the need remainder of data to reduce PK 3X
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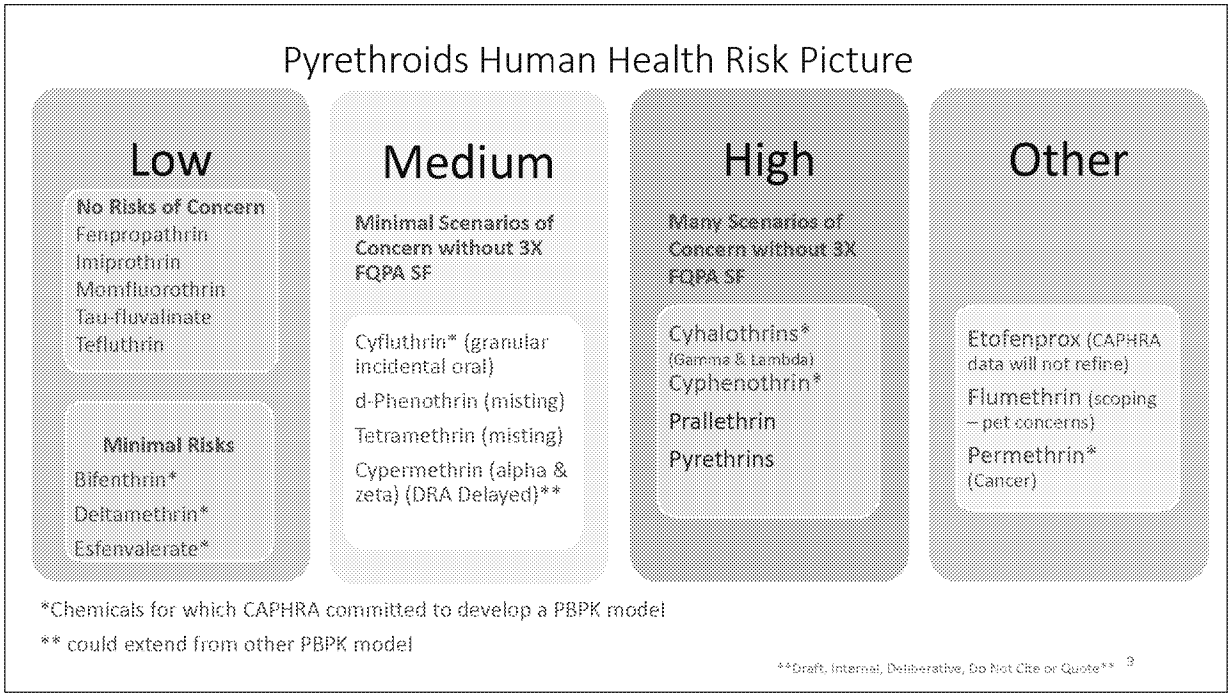

Prallethrin and pyrethrins in red because they have no PBPK models, and our current understanding is that the PBPK models anticipated cannot be extended to these

Risk – current compared to reduced SFs/UFs

Chemical	No risks of concern	Potential Human Health Risks of Concern: Residential Scenarios Post-App Kids			PBPK Model Anticipated
		# scenarios currently fail (FQPA SF of 3X)	# scenarios fail with reduced FQPA SF (to 1X)	# scenarios fail with reduced FQPA SF and other UF (to 1X)	
Fenpropathrin	X	0	0	0	
Imiprothrin	X	0	0	0	
Momfluorothrin	X	0	0	0	
Tau-fluvalinate	X	0	0	0	
Tefluthrin	X	0	0	0	
Bifenthrin		4	3	1	X
Deltamethrin [Oct. SAP]		1	0	0	X
Esfenvalerate		5	1	0	
Cyfluthrins (& beta)		5	1	0	X
d-Phenothrin (sumithrin)		1	1	1	
Tetramethrin		1	1	1	
Cyphenothrin		42	22	6	X
Cyhalothrins (gamma)		16	7	1	X
Cyhalothrins (lambda)		26	12	3	X
Prallethrin		8	5	4	
Pyrethrins		20*	20*	11	
Cypermethrin (alpha & zeta)		3	Draft Assessment	Draft Assessment	
Permethrin [Oct. SAP]		1	0	0	X

*(DB UF 10X with lack of Thyroid)

Draft, Internal, Deliberative, Do Not Cite or Quote

10

Important to note that this table is not able to account for how the POD will change. The table is based on the PODs identified in the currently available human health DRAs.

Timing Uncertainties

- Timing of SAP
  - in making a decision on FQPA safety factor for the class, and extending the model to the other pyrethroids for use in risk assessment
- How long will it take for CAPHRA to build and submit code for the second round models?
  - Best case: if data supports use of 1 model, and are completed in March 2018, models could be used for risk assessment by September 2018
  - Worst case: if there are differences between the in-vitro data and model predictions; months? years?
- Would CAPHRA do the data needed to generate models for the other high-risk cases? How long would it take?

There are still some uncertainties regarding timing. For example, we understand that there is still no date for the SAP, and we previously anticipated a SAP outcome for determination in making a decision on the FQPA safety factor for the class, as well as extending the model to the other pyrethroids.

From CAPHRA....

Environmental Fate and Effects

- Mitigation for ecological risks is not anticipated to be extensive
- Risks are well understood to be driven primarily by aquatic organisms – therefore a streamlined registration review assessment was completed for all pyrethroids undergoing registration review (~20 chemicals).
- Posted for comment in November 2016, the comment period closed in July 2017.

OPTIONS – next steps

1) PID by Sept. 2018, given current risk status
   - There are risks of concern to mitigate
2) PID by Sept. 2018, reflecting reduction of 3X FQPA SF (if all data are available and support the change)
   - The risk picture is not much different from above
3) PID after all data are submitted/reviewed/incorporated and support reduction of FQPA SF and interspecies PK factor
   - Date uncertain
4) Release refined/updated risk assessments prior to PID
   - Reflecting tox updates as CAPHRA data are available and/or exposure changes (REJV)
   - Date uncertain

These options could be applied to all pyrethroids, or just a subset.

Considerations for option 1:
Proposing mitigation for unrefined risks could be challenging to communicate with public in light of other EPA actions on insecticides (OPs/NMCs).
The mitigation needed to address the potential risks could have significant impacts, which would need review by BEAD

Appointment

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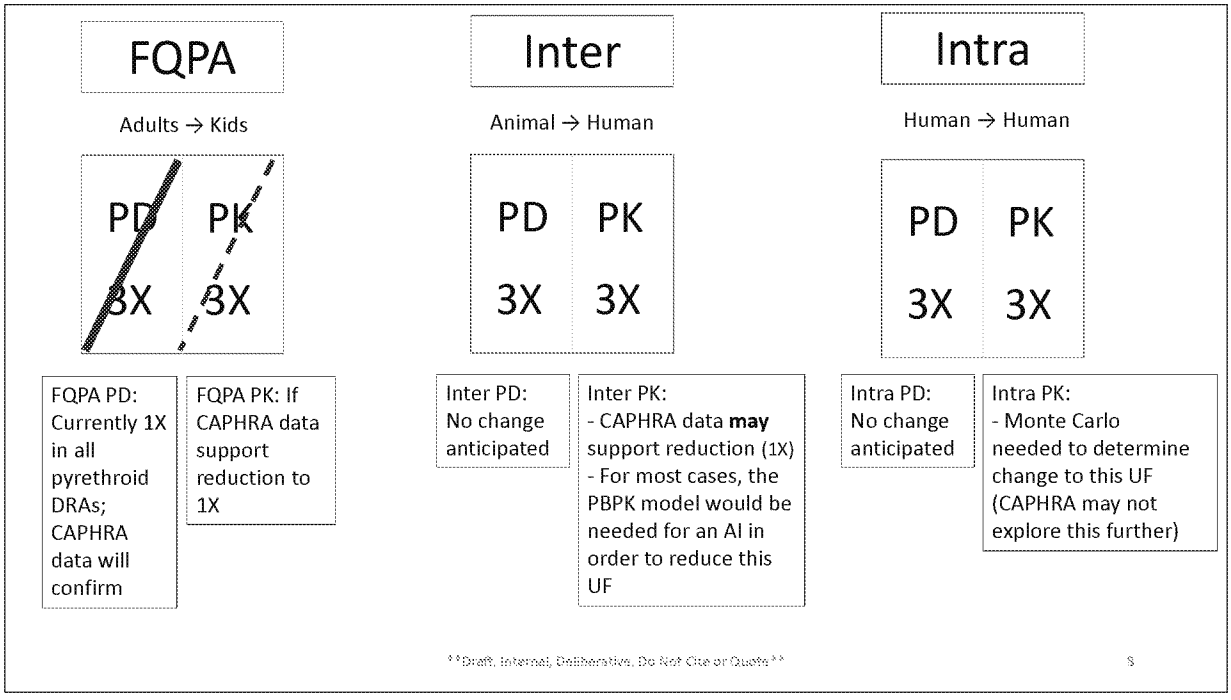

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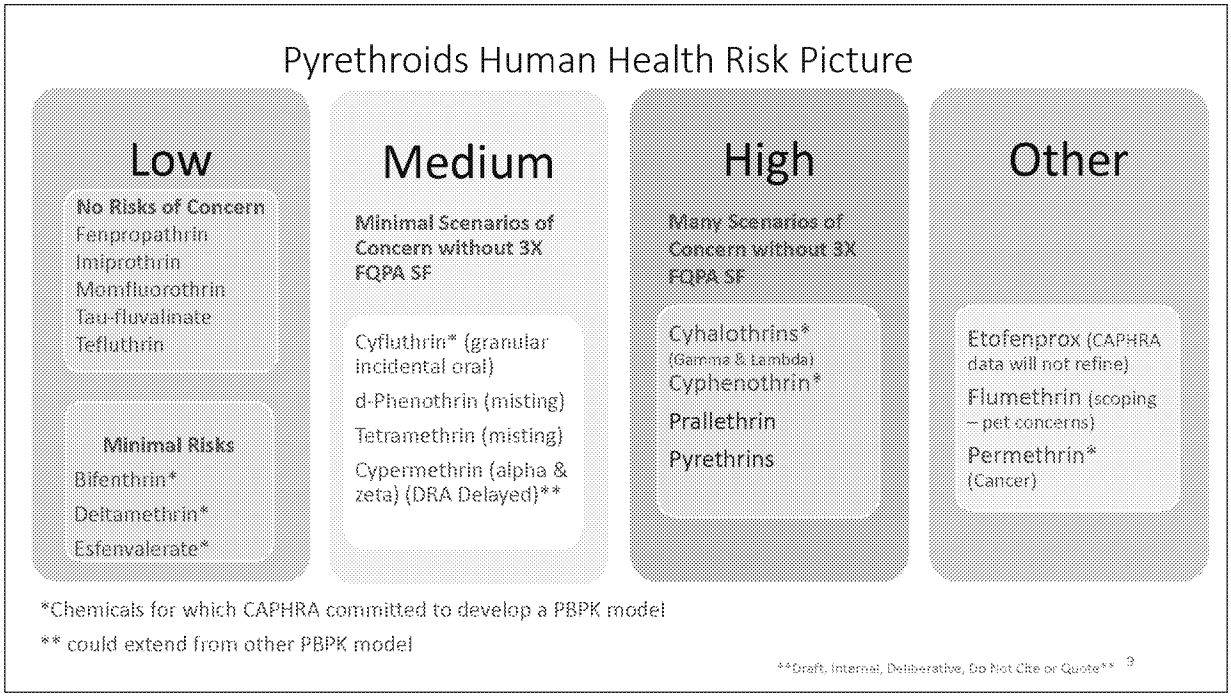

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Tefluthrin	X	0	0	0	
Bifenthrin		4	3	1	X
Deltamethrin [Oct. SAP]		1	0	0	X
Esfenvalerate		5	1	0	
Cyfluthrins (& beta)		5	1	0	X
d-Phenothrin (sumithrin)		1	1	1	
Tetramethrin		1	1	1	
Cyphenothrin		42	22	6	X
Cyhalothrins (gamma)		16	7	1	X
Cyhalothrins (lambda)		26	12	3	X
Prallethrin		8	5	4	
Pyrethrins		20*	20*	11	
Cypermethrin (alpha & zeta)		3	Draft Assessment	Draft Assessment	
Permethrin [Oct. SAP]		1	0	0	X

*(DB UF 10X with lack of Thyroid)

Draft, Internal, Deliberative, Do Not Cite or Quote

10

Important to note that this table is not able to account for how the POD will change. The table is based on the PODs identified in the currently available human health DRAs.

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- Timing of SAP
  - in making a decision on FQPA safety factor for the class, and extending the model to the other pyrethroids for use in risk assessment
- How long will it take for CAPHRA to build and submit code for the second round models?
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- Would CAPHRA do the data needed to generate models for the other high-risk cases? How long would it take?

There are still some uncertainties regarding timing. For example, we understand that there is still no date for the SAP, and we previously anticipated a SAP outcome for determination in making a decision on the FQPA safety factor for the class, as well as extending the model to the other pyrethroids.

From CAPHRA....

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- Mitigation for ecological risks is not anticipated to be extensive
- Risks are well understood to be driven primarily by aquatic organisms – therefore a streamlined registration review assessment was completed for all pyrethroids undergoing registration review (~20 chemicals).
- Posted for comment in November 2016, the comment period closed in July 2017.

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   - Reflecting tox updates as CAPHRA data are available and/or exposure changes (REJV)
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These options could be applied to all pyrethroids, or just a subset.

Considerations for option 1:
Proposing mitigation for unrefined risks could be challenging to communicate with public in light of other EPA actions on insecticides (OPs/NMCs).
The mitigation needed to address the potential risks could have significant impacts, which would need review by BEAD

Message

From: Hannah Alleman [halleman@thehcpa.org]
Sent: 2/16/2018 2:22:01 PM
To: Friedman, Dana [Friedman.Dana@epa.gov]
CC: Sara M. Stickler [sstickler@consumered.org]; Vogel, Dana [Vogel.Dana@epa.gov]; Goodis, Michael [Goodis.Michael@epa.gov]; Miller, David [Miller.DavidJ@epa.gov]
Subject: REJV - Letter to EPA Regard Use of Data
Attachments: 2018-02-15 REJV Ltr to EPA Regarding Use of Data - FINAL.PDF

Importance: High

Hello Dana,

Good morning. Please see the attached letter from the Residential Exposure Joint Venture, U.S. EPA Company Number 74888, is a consortium of companies formed under the auspices of the Household and Commercial Products Association (HCPA). HCPA was formerly known as the Consumer Specialty Products Association, Inc. (CSPA), which was rebranded on February 5, 2018. This letter is being sent with regards to the use of REJV data in the Draft Human Health Risk Assessments.

Please let me know that you have received this email and the letter. We look forward to receiving your response.

If you have any questions or concerns, please let me know.

Best,
Hannah

Hannah Alleman, PMP
Senior Project Manager, RRMC Program
Research & Regulatory Management Council
Efficient. Effective. Expert.
A Consumer Specialty Products Association Program

Office (202) 872-8110
Direct (202) 833-7318
halleman@thehcpa.org
www.rrmc.expert

Appointment

From: Jewell, Shannon [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=1862C405CF704EE692D5F61FAFF12688-JEWELL, SHA]
Sent: 9/26/2017 4:00:50 PM
To: Keigwin, Richard [Keigwin.Richard@epa.gov]; Guilaran, Yu-Ting [Guilaran.Yu-Ting@epa.gov]; Miller, Wynne [Miller.Wynne@epa.gov]; Echeverria, Marietta [Echeverria.Marietta@epa.gov]; JILL.HOLIHAN@fmc.com; John.Cummings@fmc.com; Hughes, Hayley [hughes.hayley@epa.gov]
CC: Arnold, Elyssa [arnold.elyssa@epa.gov]; Anderson, Brian [Anderson.Brian@epa.gov]; Costello, Kevin [Costello.Kevin@epa.gov]; Britton, Cathryn [Britton.Cathryn@epa.gov]; Waleko, Garland [waleko.garland@epa.gov]; Pease, Anita [Pease.Anita@epa.gov]

Subject: Pyrethroid Registration Review Status and Next Steps
Attachments: Pyrethroids presentation for ActingAA_100317 to Shannon.pptx
Location: Potomac Yard South - 12621

Start: 11/14/2017 3:00:00 PM
End: 11/14/2017 4:00:00 PM
Show Time As: Busy

11/14: Slides from this morning attached.

John Cummings RE: Meeting purpose - The object of the discussion is to review the status of the pyrethroid Registration Review cases including timelines and next steps. I don't think there is the need for a formal agenda.

Logistics email thread:

Thank you Shannon. That date and time would work well.

John

John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: Jewell, Shannon [mailto:jewell.shannon@epa.gov]
Sent: Tuesday, September 26, 2017 11:25 AM
To: John Cummings; Jill Holihan
Cc: Keigwin, Richard
Subject: RE: Tuesday's Pyrethroid Discussion

Hello John and Jill,

The November 14th date would be best on this end, as Rick's calendar is incredibly full for the month of October. Would 10am on the 14th work for you? If so, I will go ahead and schedule it on Rick's calendar.

Thank you for your understanding!

Shannon

From: John Cummings [mailto:John.Cummings@fmc.com]
Sent: Tuesday, September 26, 2017 11:16 AM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>
Cc: Jill Holihan <JILL.HOLIHAN@fmc.com>; Jewell, Shannon <jewell.shannon@epa.gov>
Subject: RE: Tuesday's Pyrethroid Discussion

Rick (and Shannon),

The following dates would work for Jill and I to hold the postponed discussion on pyrethroid registration review with you and your team. Please let us know if any of the dates would work for you and your team.

October 10
October 11
October 18
October 30
November 14

Thanks

John

John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: John Cummings
Sent: Monday, September 25, 2017 3:51 PM
To: 'Keigwin, Richard'; Jill Holihan
Subject: RE: Tuesday's Pyrethroid Discussion

Thanks Rick. I will get with Jill and we can send you some potential dates.

John

John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: Keigwin, Richard [mailto:Keigwin.Richard@epa.gov]
Sent: Monday, September 25, 2017 2:19 PM
To: John Cummings; Jill Holihan
Cc: Guilaran, Yu-Ting; Echeverria, Marietta; Miller, Wynne
Subject: RE: Tuesday's Pyrethroid Discussion

John—

Thanks for your note. I'm in Canada next week for the Global Minor Use Summit, so I think we'll need to look for some times either later in October or into November. I'll cancel tomorrow's discussion.

--Rick

From: John Cummings [mailto:John.Cummings@fmc.com]
Sent: Monday, September 25, 2017 1:59 PM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>; Jill Holihan <JILL.HOLIHAN@fmc.com>
Cc: Guilaran, Yu-Ting <Guilaran.Yu-Ting@epa.gov>; Echeverria, Marietta <Echeverria.Marietta@epa.gov>; Miller, Wynne <Miller.Wynne@epa.gov>
Subject: RE: Tuesday's Pyrethroid Discussion

Rick,

Thanks for the heads up. In speaking with Jill, we think it makes sense to postpone the meeting. It actually works out as I have quite a few things going on tomorrow with the DuPont deal. Jill and I are both available next Tuesday (10/3) if that would work for you and your team.

Thanks

John

John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: Keigwin, Richard [mailto:Keigwin.Richard@epa.gov]
Sent: Saturday, September 23, 2017 8:20 AM
To: John Cummings; Jill Holihan
Cc: Guilaran, Yu-Ting; Echeverria, Marietta; Miller, Wynne
Subject: Tuesday's Pyrethroid Discussion

John and Jill—

I just learned that I need to attend a meeting with our Acting Deputy Administrator to discuss some budget related issues. As a result, I will not be able to join you for Tuesday's planned discussion at 1pm. I believe that Yu-Ting, Marietta, and Wynne are still available.

My apologies for the late notice.
--Rick

Rick Keigwin
Director, Office of Pesticide Programs
US Environmental Protection Agency

Click here to report this email as spam.

Pyrethroid Registration Review Status

November 14, 2017

Intent of the current version of the slides – to give a brief overview of CAPHRA history, timeline, and research status, as well as potential impact on regulatory decision-making. Moving forward with upper level briefings, recent conversations seem to indicate interest in the technical details of what brought us to this point…history of tox data, SAPs – how to proceed?

Overview

- Council for Advancement of Pyrethroid Human Risk Assessment (CAPHRA)
  - History, timeline, and research status
- Implication of CAPHRA research on regulatory decision-making
- Current versus potential status of pyrethroid human health risk
- Timing Uncertainties
- Ecological Risk Assessment Status
- Options/next steps

Exploration of Juvenile Sensitivity to Pyrethroids

- September 2009 – DNT not providing the data needed to assess comparative lifestage sensitivity concerns
  - Studies showing differences in the sensitivity of young rats (at high doses, dose over time, differences decreasing rapidly with age)
  - Limited available data (on doses affecting the startle response and PK)
- February 2010 – EPA solicits protocols from pyrethroid companies for review by FIFRA SAP in July 2010
- July 2010 SAP – Pyrethroid and Pyrethrins Technical Working Group (named was changed to the *Council for the Advancement of Pyrethroid Human Risk Assessment* or *CAPHRA in 2011*) submits protocol, and SAP provides feedback
- October 2011 - Pyrethroid Cumulative
  - EPA retains FQPA 3X for pharmacokinetics (PK), 10X for interspecies variability, 10X for intraspecies variability

Beginning with Sept. 2009 determination laid out in a letter to registrants, that DNTs were not providing the data needed to assess comparative lifestage sensitivity.

EPA solicits protocols designed to address this question in February 2010, and for discussion at a July 2010 SAP.

Additional info:
Following the 2010 SAP on the proposal, CAPHRA revised their protocol (to evaluate the potency of pyrethroids to human sodium channels and transplantation of adult & juvenile rat synaptic membrane into oocytes, in addition conducting targeted in vivo studies on behavioral metrics and developing PBPK models)
SAP charge questions:
appropriateness of the ASR technique as a measure of pyrethroid induced toxicity, including suggestions to assure quality of the study design and resulting data
Are there alternative approaches potentially requiring less time than the PBPK effort for evaluating the potential for post-natal sensitivity that could be used by the Agency

EPA Meetings with CAPHRA

- August 9, 2012 – Technical and Management Update
- November 27, 2012 – Status Update
- February 7, 2013 – Technical and Management Update
- November 7, 2013 – Technical and Management Update
- February 18, 2014 – Status Update
- September 5, 2014 – Technical and Management Update
- December 3, 2014 – Technical Working Meeting (RTP)

Not an exhaustive list of all meetings or phone calls, but highlights the regularity of our check-ins with CAPHRA on their research program and status. In addition to status updates with a few individuals from PRD and HED, there were a number of technical updates for HED, as well as PMRA and DPR, and mgmt. updates for DDs and an a couple of occasions with the OD.

Meetings, Submissions, and SAPs

- May 2015 SAP – Research to Evaluate the Potential for Juvenile Sensitivity to Pyrethroids
- October 27, 2015 – Status Update
- December 10, 2015 – Status Update
- February 10, 2016 – Status and Technical Update
- July 12, 2016 – Status Update
- September 13, 2016 – Status Update
- December 1, 2016 – EPA meets with CAPHRA to discuss upcoming PBPK SAP (originally scheduled for October 24 – 27, 2017)
- January 2016 (through May 2016) – 35 reports (permethrin, deltamethrin physiological parameters)

In addition to those ongoing updates, there was also the May 2015 SAP where the Agency sought the FIFRA SAP's advice on the current state of the science with the CAPHRA research effort and proposals for next steps including the extension of data on deltamethrin and permethrin to other pyrethroids.

Panel noted several concerns for CAPHRA to address moving forward, but supported CAPHRA's efforts to develop a human PBPK model as being on the right track for addressing the information needed by the agency to address potential juvenile sensitivity.

We continued with status updates and check-ins, through CAPHRA submissions in preparation for the PBPK SAP…

Milestones	Timeline provided 1/12/2012	Timeline provided 9/25/2014	Timeline provided 12/8/2015	Current status
Part 1 - Neurotoxicology				
Acoustic Startle Response	TBD	TBD	4/16	Submitted 10/5/17
Human Ion Channels	2/12	1/15	1/16	Submitted 5/5/16
Neurolemma	6/12	1/15	4/16	Report submitted 10/17; raw data needed for statistical validation, not yet submitted
Part 2 – Model Development (permethrin and deltamethrin)				
PBPK Code	12/12	Mid-2015	4/16	Code for SAP submitted 3/17; acknowledgement submission is not final code 8/17; final code not yet submitted
Part 3 – Model parameterization (5 additional pyrethroids)				
Chemical-specific Parameterization	12/13	TBD	9/16	"Acknowledgement of evolving parameter database" in 9/6/17 email, 3/18?

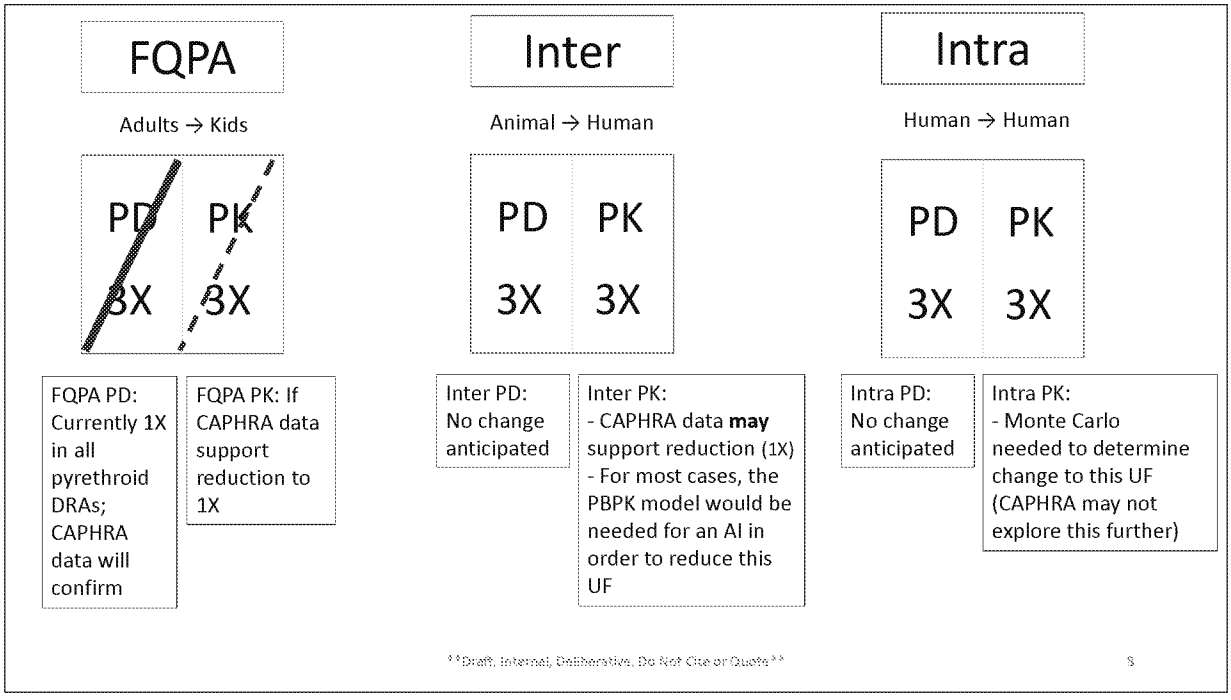
There are a number of milestones involved in CAPHRA's research program, but I wanted to highlight a few of the items, like the acute startle and neurolemma work, which have been the topic of many discussions over the years, and their shifting timeframes.

Looking at the right-hand column "current status," there are still some outstanding items including data needed for statistical validation of the neurolemma work, the final PBPK code for permethrin and deltamethrin, and the chemical-specific data needed to parameterize the model for the additional 5 pyrethroids.

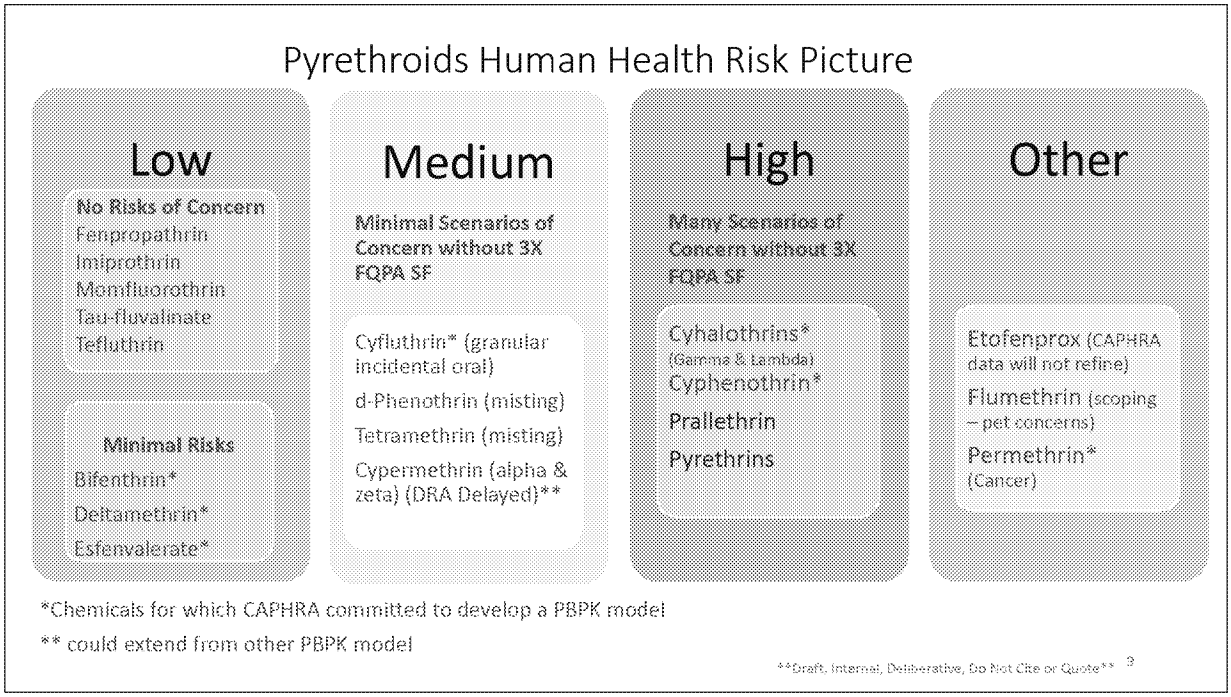
Potential Impact of CAPHRA Data

- POD likely to change for chemicals with PBPK models
- FQPA safety factor may change for the class
- Interspecies factor may change for chemicals with PBPK models

Before moving forward, we just wanted to highlight the potential impact of the CAPHRA data as is currently understood.



FQPA – Neurolemma and acoustic startle will be important in confirming removal of 3X PD; and the need remainder of data to reduce PK 3X
Interspecies – PBPK models for each of the pyrethroids CAPRHA committed to producing is likely to reduce the PK
Intraspecies – uncertainty – we are not sure if CAPHRA will explore this further



Prallethrin and pyrethrins in red because they have no PBPK models, and our current understanding is that the PBPK models anticipated cannot be extended to these

Risk – current compared to reduced SFs/UFs

Chemical	No risks of concern	Potential Human Health Risks of Concern: Residential Scenarios Post-App Kids			PBPK Model Anticipated
		# scenarios currently fail (FQPA SF of 3X)	# scenarios fail with reduced FQPA SF (to 1X)	# scenarios fail with reduced FQPA SF and other UF (to 1X)	
Fenpropathrin	X	0	0	0	
Imiprothrin	X	0	0	0	
Momfluorothrin	X	0	0	0	
Tau-fluvalinate	X	0	0	0	
Tefluthrin	X	0	0	0	
Bifenthrin		4	3	1	X
Deltamethrin [Oct. SAP]		1	0	0	X
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The mitigation needed to address the potential risks could have significant impacts, which would need review by BEAD

Message

From: Cindy Smith [csmith@gowanco.com]
Sent: 1/30/2020 3:32:12 PM
To: Keigwin, Richard [Keigwin.Richard@epa.gov]
Subject: Submission
Attachments: Coalition of OP Registrant EPA Submission Jan 30 2020.pdf

Rick here is the paper pulled together by Exponent. Thanks Cindy

Coalition of OP Registrants

Managed by B&C® Consortia Management, L.L.C.

ADAMA USA ◆ AMVAC CHEMICAL CORPORATION
BAYER US LLC ◆ FMC CORPORATION ◆ GOWAN COMPANY

January 30, 2020

Via E-Mail

Mr. Rick Keigwin, Jr.
Director
U.S. Environmental Protection Agency
Office of Pesticide Programs
Division Mail Code (7501P)
1200 Pennsylvania Ave. NW
Washington, D.C. 20460

Re: Assessment of the 2015 OP FQPA Factor Determination Based on New Information

Dear Mr. Keigwin:

The Coalition of Organophosphate (OP) Registrants is submitting the attached document for consideration by the United States Environmental Protection Agency (EPA). Based on the information in this submission, additional data that EPA now has regarding OPs and other arguments that have been provided via open dockets for individual OP active ingredients, we are requesting that EPA revisit the Health Effects Division (HED) 2015 Literature Review titled "Literature Review on Neurodevelopmental Effects and FQPA Safety Factor Determination for the Organophosphates" referred to in this document as the "Literature Review". We believe the overwhelming weight of evidence supports that a Food Quality Protection Act (FQPA) 10x is not justified for all OPs.

The epidemiology data that EPA relied upon in the Literature Review has serious flaws that make them inappropriate for use in a risk assessment, including the basis for reinstating an FQPA 10x on all OPs.

First, HED has acknowledged that there is no plausible biological explanation for the reported neurodevelopmental associations. In the absence of an experimentally demonstrable and accepted common mode of action/adverse outcome pathway, there is no basis for bridging any of the exposure outcomes alleged in the epidemiology studies from one OP to another. The only accepted common mode of action for the OPs is cholinesterase inhibition. There remains no scientifically valid evidence that demonstrates that regulating the OPs based on red blood cell cholinesterase is not protective for all effects of concern including neurodevelopmental effects.

2200 PENNSYLVANIA AVENUE, N.W. ◆ SUITE 100W ◆ WASHINGTON, D.C. 20037 ◆ TEL 202.557.3800 ◆ FAX 202.557.3836

Second, and consistent with EPA's response to the 9th Circuit court, despite numerous attempts, the researchers at Columbia University have refused to provide EPA with the information necessary to validate the studies and provide any credible evidence of neurodevelopmental effects that is sufficiently valid, complete and reliable to meet the standards under the Federal Food, Drug, and Cosmetic Act (FFDCA).

Additionally, in the Literature Review, the link to the OPs is very weak and not scientifically valid. It is based on spot samples of non-specific urinary metabolites. Reported associations that are based on nonspecific dialkly phosphate biomarkers (DAPs) are inappropriate for use in regulatory decision-making. There is no way to track the DAP biomarkers to any specific OP, moreover the presence of the urinary DAPs may simply reflect exposure to preformed metabolites that can be present in foods and in the environment at higher levels than parent molecules and can seriously confound interpretation of the urinary DAP data. Because the reported urinary DAP data are not reliable, the reported association are also not reliable. EPA correctly recognized this deficiency with common urinary biomarker data in its review of epidemiological data for the pyrethroids.

With this submission, other submissions and additional data, we believe we have provided EPA with sufficient information to revisit the conclusions of the Literature Review and to not finalize any OP risk assessment that results in unnecessary loss or restriction of uses without consideration of all of this information. Thank you for your consideration.

Sincerely,

Cindy Smith

Cindy Smith
Chair, Coalition of OP Registrants

Enclosure

Exponent
1150 Connecticut Ave, NW
Suite 1100
Washington, DC 20036

telephone 202-772-4900
facsimile 202-772-4979
www.exponent.com

TITLE:
Assessment of the 2015 OP FQPA Factor Determination Based on New Information

DATA REQUIREMENTS:
Not Applicable

AUTHORS:
Rick Reiss, ScD
Nelson Pace, PhD

COMPLETED ON:
January 29, 2020

SPONSOR:
Coalition of OP Registrants
2200 Pennsylvania Avenue, N.W., Suite 100W
Washington, D.C. 20037

PROJECT IDENTIFICATION:
1906771.000 - 8928

STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality, on any basis whatsoever, is made for any information contained in this document. I acknowledge that information not designated as within the scope of FIFRA §10(d)(1)(A), (B), or (C) and which pertains to a registered or previously registered pesticide is not entitled to confidential treatment and may be released to the public, subject to the provisions regarding disclosure to multinational entities under FIFRA 10(g).

COMPANY: Coalition of Organophosphate (OP) Registrants

SUBMITTER: Cindy Smith January 29, 2020

Date

STATEMENT OF COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

This report is a review of existing data. Good Laboratory Practice Standards, 40 CFR Part 160, are not applicable to this submission.

AUTHORS:

January 29, 2020

Date

January 29, 2020

Date

SPONSOR & SUBMITTER:

Cindy Smith

January 29, 2020

Date

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List of Tables

Executive Summary

In 2015, the U.S. Environmental Protection Agency (EPA) reviewed literature on potential neurodevelopmental effects and birth outcomes for organophosphate (OP) pesticides and concluded that "…there is sufficient uncertainty in the human dose-response relationship for neurodevelopmental effects which prevents the agency from reducing or removing the statutory 10X Food Quality Protection Act (FQPA) Safety Factor." From this finding, EPA elected to reinstate the default FQPA 10X factor and has subsequently applied it in draft risk assessments for individual OPs.

After publishing its 2015 literature review OP pesticides, EPA issued guidelines on conducting systematic reviews of epidemiologic studies and applied these guidelines in a review of pyrethroid epidemiologic studies. The pyrethroid review includes many of the same studies and other studies of similar design. However, the pyrethroid review employed more rigorous criteria for classifying studies as "high quality" than did the OP review. In particular, the pyrethroid review assigned substantially more negative weight to studies that relied on spot samples of non-specific urinary metabolites to estimate exposures.

The exposure assessment methodology for most of the OP and pyrethroid studies is similar. Both the OP and pyrethroid studies measure urinary levels of non-specific metabolites (i.e., multiple OP and pyrethroids metabolize to the same metabolites, respectively). The limitations of these exposure biomarkers include: (1) the metabolites are not specific to individual chemicals and the potency of the chemicals in the OP and pyrethroid classes vary widely, (2) the studies only include one or two measurements during pregnancy despite wide variability in concentrations across time, so the spot samples likely do not reflect longitudinal exposure, and (3) the same metabolites formed in humans also form on plants or can be found in the environment, so measurement of metabolites in urine does not necessarily mean that there was direct exposure to an OP.

The following same or similar studies were reviewed differently in the OP and pyrethroid reviews:

- Oulhote and Bouchard (2013) were both reviewed in the OP and pyrethroid documents and the OP review classified it as "medium quality," while the pyrethroid review classified it as "low quality."

- Furlong et al. (2017a) in the pyrethroid review and Furlong et al. (2014) in the OP review are both studies of children's behavior and executive function in association with maternal exposure during pregnancy in the Mt. Sinai New York cohort. The OP review

classifies Furlong et al. (2014) as "high quality" and the pyrethroid review classifies Furlong et al. (2017a) as "low quality."

- The Quiros-Alcala et al. (2014) and Wagner-Schuman et al. (2015) studies in the pyrethroid review and the Bouchard et al. (2010) study in the OP review are both cross-sectional studies that assess metabolites in a single spot urine sample in association with parent-reported attention-deficit/hyperactivity disorder in the National Health and Nutritional Examination Survey (NHANES). The OP review classifies Bouchard et al. (2010) as "high quality," and the pyrethroid review classifies Quiros-Alcala et al. (2014) and Wagner-Schuman et al. (2015) as "low quality."

- Watkins et al. (2016) in the pyrethroid review and Fortenberry et al. (2014) in the OP review are both studies of neurodevelopmental outcomes in the same 187 subjects in Mexico City in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study. The OP review classified Fortenberry et al. (2014) as "high quality" and the pyrethroid review classified Watkins et al. (2016) as "low quality."

A careful review of the OP and pyrethroid document shows that the primary reason for the difference in classification between the same or similar studies was the exposure assessment study quality.

A literature search was also conducted by Exponent to determine if significant literature was published after the 2015 OP review. There were 39 relevant studies identified, of which 31 were related to neurodevelopment effects, which EPA cited as the basis for the FQPA decision. A systematic review of the entire body of literature using the most current study ranking criteria is necessary; however, it is noted a number of new, large studies that do not report associations with OP metabolites are included in the new literature.

It is recommended that EPA revisit the literature review in light of the information provided in this document, the 2016 guidance regarding review criteria for epidemiology studies and other data submitted to the agency related to organophosphates.

Introduction

The U.S. Environmental Protection Agency (EPA) released a literature review on neurodevelopmental effects and birth outcomes in 2015 for organophosphate (OP) pesticides (U.S. EPA, 2015). This document reviews new information that has become available since the 2015 OP review.

The OP review surveyed epidemiologic literature and corresponding evidence for effects in animal studies. It concluded that there was sufficient evidence for neurodevelopmental effects but not birth outcomes. Given this conclusion, EPA determined that the Food Quality Protection Act (FQPA) 10X safety factor "will be retained for OPs for the population subgroups that include infants, children, youth, and women of childbearing age for all exposure scenarios." Prior to this decision the OPs had their FQPA safety factor reduced to 3X or 1X based on GLP animal toxicity data. In subsequent OP risk assessments, the FQPA 10X factor has been applied.

Since publication of the OP review, EPA has published new guidelines for conducting systematic reviews of epidemiologic literature (U.S. EPA, 2016). It applied those guidelines in reviewing the epidemiologic literature for pyrethroids (U.S. EPA, 2019). The pyrethroid review found "little substantive evidence to suggest a clear associative or causal relationship between exposure to pyrethroids and cancer and non-cancer health endpoints." For neurodevelopmental effects, the OP and pyrethroid reviews included some key studies from the same cohorts. Other studies considered in the OP and pyrethroid reviews are broadly similar in design. Generally, the OP and pyrethroid studies measure urinary biomarker measurements during pregnancy as surrogates for exposure and evaluate subsequent outcomes in the children of the mothers. This document compares how EPA reviewed the same or similar studies for OPs and pyrethroids to evaluate the consistency of the reviews and to determine if different criteria for study quality in the OP and pyrethroid reviews affected how studies were classified in regards to overall quality.

EPA finished the OP review in 2015 and considered 9 other studies in their response to the comments (U.S. EPA, 2016). Since that time, there are nearly 40 relevant studies published that would have met the criteria for inclusion in the EPA OP review. The EPA OP review evaluated 38 studies, classifying 8 as "high quality," 15 as "medium quality," and 15 as "low quality." Therefore, the new literature published since 2015 is similar in size to the literature considered in the 2015 EPA review. This document summarizes the scope of the literature published since 2015. A systematic review under EPA's 2016 guidelines may be conducted later.

Comparison of OP and Pyrethroid Reviews

Criteria for Study Quality Assessment

The OP FQPA literature review was conducted in 2015 before EPA had established guidance on systematic reviews. The following text from the document describes the process used by EPA for the OP FQPA literature review (key highlights in italics):

> "In recent years, the National Academy of Sciences has encouraged the agency to move towards systematic review processes to enhance the transparency of scientific literature reviews that support chemical-specific HHRAs to inform regulatory decision making. The NRC defines systematic review as "a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies". Consistent with NRC's recommendations, *EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) is currently developing systematic review policies and procedures*. In short, OCSPP employs fit-for-purpose systematic reviews that rely on standard methods for collecting, evaluating and integrating the scientific data supporting the agency's decisions. The literature review *described here uses concepts consistent with systematic review* such as detailed tracking of search terms and which literature have been included or excluded." *(Italics* added).

The text makes clear that at the time of the OP FQPA review, OPP was working on, but had not yet completed, guidelines on systematic review and that the OP FQPA review "uses concepts consistent with systematic review" as opposed to following formal guidelines.

EPA OPP published a *Framework for Incorporating Human Epidemiologic and Incident Data in Risk Assessments for Pesticides* in 2016 (U.S. EPA, 2016), a year after the OP review was published. This guidance was followed in the 2019 pyrethroid review. The 2016 guidance applied in the pyrethroid review contains significantly different criteria for evaluating exposure assessment in epidemiologic studies as elaborated on below.

The OP and pyrethroid FQPA reviews each contain a table with criteria for evaluating study quality for different categories (Table 2.2.4-1 in the OP review and Table 2 in the pyrethroid review). The OP review includes categories for (1) study design, (2) exposure assessment, (3) outcome assessment, (4) confounder control, (5) statistical analysis, and (6) risk of (other) bias (selection, differential misclassification, effect size magnification, other). The pyrethroid review includes all of these categories except study design. For the categories apart from study design, the description of the study quality criteria are identical to the OP review, except for exposure assessment.

For study design, the OP review includes the following descriptions:

- High: Prospective, exposure precedes disease
- Moderate: Case control
- Low: Cross-sectional, Ecological

These descriptors are non-controversial and appear consistent with the pyrethroid review, even though the pyrethroid review did not include them as specific study quality criteria.

For exposure assessment, the OP and pyrethroid reviews provide significantly different descriptions. As discussed later, there are inconsistencies in the assessment of the same or similar studies in the OP and pyrethroid reviews and one of the key reasons for the differences is how the exposure assessment in the study was evaluated. Table 1 compares the text for the study quality criteria for exposure assessment as presented in the two review.

Table 1. Review of study quality criteria in the OP and pyrethroid reviews

Parameter	High	Moderate	Low
OP review (U.S. EPA, 2015)	Exposure assessment includes information on specific OP a.i.'s (e.g., CPF, MAL), or urinary metabolite (TCPy, IMPy), or high quality questionnaire based chemical specific exposure assessment during relevant exposure	Non-specific biomarker of exposure (DAP), or effect (AChE/BuChE), or questionnaire based individual level information on the OP class, or sub-class	Low quality questionnaire based exposure assessment, or ecologic exposure assessment, with or without validation
Pyrethroid review (U.S. EPA, 2019)	Accurate and precise quantitative relationship with external exposure, internal dose, or target dose, possibly associated with a MOA/AOP. If questionnaire utilized, questionnaire and/or interview answered by subjects for chemical-specific exposure	Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose, or target dose. Questionnaire and/or interview for chemical-specific exposure answered by subjects or proxy individuals	Poor surrogate, low-quality questionnaire and/or interview; information collected for groups of chemicals rather than chemical-specific; no chemical-specific exposure information collected; ever/never use[1] of pesticides in general evaluated

[1] Classifying subjects by whether they used or did not use pesticide without regard to duration and frequency of use.

The descriptors for study quality used in the pyrethroid review are the same as in the 2016 guidance. Thus, the source of the change in the exposure assessment study quality criteria is the 2016 guidance.

There are clear differences in the study quality criteria for exposure assessment between the OP and pyrethroid reviews. Before discussing the differences, it is necessary to briefly review how the exposure assessment is conducted in most of the OP and pyrethroid studies. For OPs, the most common biomarker is a series of six urinary dialkylphosphates (DAPs). DAPs are non-specific OP metabolites that derived from some but not all OPs. For pyrethroids, there are a series of six urinary biomarkers (see Table 4 of U.S. EPA, 2019) that are metabolites of multiple pyrethroids.

Both the OP and pyrethroid biomarkers have a similar set of limitations:

- The biomarkers are non-specific to a single chemical and the potency of the chemicals in the OP and pyrethroid classes varies widely.

- Often there is only a single urine sample collected during pregnancy despite wide variability in exposure over time. Bradman et al. (2013) collected consecutive samples over 7 days for 25 children. The variability over 7 days was substantial with most subjects having daily measurements at least an order of magnitude apart and some subjects have daily samples as much as three orders of magnitude apart. The 2016 guidance states that "While biomonitoring has many advantages over others exposure assessment methods, it also has its own limitations. In many studies, biological sample are only taken from a single point in time and may not reflect accurately reflect longitudinal patterns, particularly if exposures are highly variable." The DAP biomarker is clearly "highly variable". Thus, the biomarkers likely do not reflect longitudinal exposure over pregnancy, which is noted in the pyrethroid review of individual biomarker studies.

- Both the OP and pyrethroid metabolites are considered to be of low toxicity and are formed on plants leading to direct exposure to the metabolites. This leads to uncertainty in the portion of urinary metabolite that is due to direct exposure of the OP or pyrethroid or the metabolite itself. Zhang et al. (2008) found that the molar ratio of DAPs/OPs ranged from 0.02-73 in 153 produce samples. Thus, there can be large differences between DAPs and OPs and DAPs can sometimes be higher than OPs and vice versa. The large range results in large imprecision in using DAPs as a surrogate for OP exposure.

In the OP review, the use of a "non-specific biomarker" such as DAPs is considered to be of "moderate quality" for exposure assessment. For pyrethroids, the "moderate quality" criteria are much different. Instead of a "non-specific biomarker," a "moderate quality" biomarker must have a "relationship between the biomarker in a specified matrix and external exposure, internal dose, or target dose" and questionnaire data need to be "chemical-specific." In contrast, the "low quality" category for pyrethroids includes instances where "no chemical-specific exposure information [was] collected." For urinary DAPs, which are not specific to any OP, a "low quality" classification results from applying the criteria in the 2016 guidance and 2019 pyrethroid review.

Furlong et al. (2017a) is an example of a study using a non-specific urinary biomarker where the overall study quality was rated as low in the pyrethroid review. The study utilized single spot samples of three pyrethroid urinary metabolites for exposure assessment. The pyrethroid review states:

> "… a major limitation of the study was that pyrethroid exposure was assessed by measuring urinary pyrethroid metabolites in a single spot urine sample during pregnancy. This approach may not accurately reflect longitudinal exposure patterns and may also be reflective of exposure to non-toxic, environmental degradants/metabolites that may be present in the environment and food."

Similar language is repeated for several of the study reviews. However, EPA did not characterize this methodological limitation as "major" in the OP review. Instead, EPA minimized the problem by remarking that any exposure misclassification was probably random with respect to outcomes. In fact, the misclassification may not be random—for example, dietary intake of metabolites on fruits and vegetables may differ by health status—and even if it is random, it may not lead predictably to underestimated associations (Rothman and Greenland, 1998).

In contrast to how the pyrethroid review viewed the limitations of the urinary biomarker measurements, 6 of the 8 studies rated as "high quality" in the OP review included a non-specific OP biomarker. Of these, 4 studies used a single spot urine sample and 2 studies had 2 spot urine samples. Given the more than order of magnitude variability in samples taken across one week in the Bradman et al. (2013) study, two samples are insufficient to estimate longitudinal exposure.

The 2016 guidance additionally has a Tier 1 and Tier 2 classification for exposure biomarkers as follows:

- Tier 1: Biomarker has accurate and precise quantitative relationship with external exposure, internal dose, or target dose.
- Tier 2: Biomarker has an unknown quantitative relationship with external exposure, internal dose, or target dose or is poor surrogate (low accuracy and precision) for exposure/dose.

The DAP biomarker is clearly in Tier 2 given the limitations noted above.

Evaluation of Ratings for the Same or Similar Studies

The same or similar studies were rated differently in the OP and pyrethroid reviews by EPA, and the key reason for the differences was differing assessments of the exposure assessment quality.

Oulhote and Bouchard (2013) in Both OP and Pyrethroid Reviews

Oulhote and Bouchard (2013) is a cross-sectional study of data from the Canadian Health Measures Survey (CHMS). It investigated associations between urinary OP biomarkers (DAPs) and pyrethroid biomarkers (5 non-specific metabolites) and parentally-reported behavioral problems among a representative sample of Canadian children aged 6-11 years old. The OP review rated the study as "medium quality" and the pyrethroid review rated the study as "low quality." The pyrethroid review states:

> "The quality of the study was ranked low. CHMS provides comprehensive monitoring of the Canadian population's health and health habits, but is based on a cross-sectional study design. As such, CHMS cannot assess the temporal association between pyrethroid exposure and neurobehavior. In addition to this limitation, the CHMS only obtained a single spot urine sample collected throughout the study. This approach may not accurately reflect longitudinal exposure patterns and may also be reflective of exposure to non-toxic, environmental degradants/metabolites that may be present in the environment and food."

Thus, the main limitations noted in the pyrethroid review are the cross-sectional design and the use of a single spot urinary metabolite measurement for exposure. The OP review cites a cross-sectional design as low quality despite rating the overall study quality as "medium quality," so the principal reason for the difference in classification between the OP and pyrethroid reviews was difference in how the two reviews rated the quality of exposure assessment.

Furlong et al. (2014) in the OP Review and Furlong et al. (2017a) in the Pyrethroid Review

Furlong et al. (2017a) in the pyrethroid review and Furlong et al. (2014) in the OP review are both studies of children's behavior and executive function in association with maternal exposure during pregnancy in the Mt. Sinai New York cohort. Both the OP and pyrethroid studies use non-specific urinary metabolites for exposure assessment. Despite being from the same cohort and using essentially the same methods, the pyrethroid review rated the study as "low quality" whereas the OP review rated the study as "high quality." The pyrethroid review states:

> "The quality of the study was ranked low. The primary strengths of the study were its prospective study design, and the longitudinal assessment of neurobehavioral development. While the study had several strengths, a major limitation of the study was that pyrethroid exposure was assessed by measuring urinary pyrethroid metabolites in a single spot-urine sample during pregnancy. This approach may not accurately reflect longitudinal exposure patterns and may also be reflective of exposure to non-toxic, environmental degradants/metabolites that may be present in the environment and food. In addition, only 162 of the 361 enrolled study subjects remained in the study after follow-up, resulting in a relatively low participation rate of only 45%. The investigators also reported that study participants that remained at follow-up were more likely to have pyrethroid biomarker levels below the LOD. Specifically, participation rates stratified by biomarker and whether levels were above the LOD were: 3-PBA (36% > LOD vs 48% < LOD); *cis*-DCCA (29% > LOD vs 48% < LOD); and *trans*-DCCA (28% vs 49%). This suggests that selection bias may be present in the study because exposed subjects were more likely to drop out of the study. In addition, multiple comparisons were made with no provision for statistical adjustment in the reported findings. Finally, the investigators were also unable to evaluate dose-response relationships due to the small numbers of participants with detectable pyrethroid metabolite levels. Finally, no laboratory or neurodevelopmental assessments QA/QC information was made available or evidenced."

The primary reasons for the "low" rating in the pyrethroid review are the use of single spot samples of urinary metabolites for exposure assessment, loss to follow-up, high number of non-detects, lack of correction for multiple comparisons, and lack of QA/QC information. While there were a lower number of non-detects for OPs (only 3% with detections of no DAPs) compared to pyrethroids (70-84% depending on metabolite), the other study limitations noted in the pyrethroid review apply to the OP review as well. For both OPs and pyrethroids, the effect testing is done by comparing subjects with a ten-fold higher exposure compared to others. The study does not include a full dose-response assessment. Therefore, the difference in non-detections does not justify the stark ("low" vs. "high") difference in rating.

Bouchard et al. (2010) in the OP Review and Quiros-Alcala (2014) and Wagner-Schuman et al. (2015) in the Pyrethroid Review

The Quiros-Alcala et al. (2014) and Wagner-Schuman et al. (2015) studies in the pyrethroid review and the Bouchard et al. (2010) study in the OP review are both cross-sectional studies that assess metabolites in a single spot urine sample in association with parent-reported attention-deficit/hyperactivity disorder in the National Health and Nutritional Examination Survey (NHANES). Again, despite using basically the same population (in different survey years) and methods, EPA rated the Quiros-Alcala et al. (2014) and the Wagner-Schuman et al. (2015) studies as "low quality" in the pyrethroid review and the Bouchard et al. (2010) study as "high quality." The pyrethroid review described the study quality:

> "The quality of the study was ranked low. An adequate sample size was considered a strength of this study. A major limitation of the study included the poor outcome ascertainment. The identification of cases was solely based on interviewed responses by the parents which might have resulted in outcome misclassification. Furthermore, the parental responses were based on only two interview questions that defined the outcome of interest. Additional limitations included the cross-sectional design of the study and the use of a single spot urine sample. This approach may not accurately reflect longitudinal exposure patterns and may also be reflective of exposure to non-toxic, environmental degradants that may be present in the environment and food."

The major limitations included the lack of an independent outcome classification, the cross-sectional design, and the use of a single spot urinary metabolite sample. These limitations apply equally to the OPs and pyrethroids.

Fortenberry et al. (2014) in the OP Review and Watkins et al. (2016) in the Pyrethroid Review

Watkins et al. (2016) in the pyrethroid review and Fortenberry et al. (2014) in the OP review are both studies of neurodevelopmental outcomes in the same 187 subjects in Mexico City in the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study. Again, even though these analyses use the same study populations and mostly the same methods—and, in fact, the Fortenberry study might be considered weaker due to its reliance primarily on parent-reported outcome measures, whereas the Watkins study evaluated outcomes assessed by trained research personnel—the pyrethroid review rates the Watkins et al. (2016) study as "medium quality," whereas the OP review rates Fortenberry et al. (2014) as "high quality." The pyrethroid review described the study quality:

> "The quality of the study was ranked moderate. Study strengths included the cohort study design, the care taken in transporting the collected urine samples (*i.e.,* transported on dry ice), and the neurodevelopment assessments used to determine

potential developmental delays within the study. Study limitations included the measured 3-PBA metabolite concentrations being below the limit of detection for more than half of all study participants and the use of a single maternal spot-urine sample to assess long-term exposure. This approach may not accurately reflect longitudinal exposure patterns and may also be reflective of exposure to non-toxic, environmental degradants and metabolites that may be present in the environment and food. Furthermore, the medium and high 3-PBA metabolite levels were not reported by the study authors. Additionally, no information on laboratory QA/QC procedures or results was provided."

Again, the pyrethroid review highlights the use of single spot urinary metabolite sample as well as a low rate of detects and a lack of QA/QC procedures. While the low rate of detects is not applicable to OP study, the other issues are relevant.

Quality Control/Quality Assurance

The pyrethroid review discusses quality assurance/quality control (QA/QC) procedures in chemical and outcomes measurements, and faults many of the studies for providing no or minimal information about how their sampling protocols and analytical methods were designed, if at all, to minimize the potential for sample contamination and measurement error. The OP review spends little effort in addressing these important issues; the term "quality control" is used only once in reference to outcome assessment in a single study, and QA/QC of exposure measurements is not discussed.

Literature Published Since the 2015 OP Review

We conducted a PubMed search for literature published after the 2012 OP review. The following search terms were used:

(organophosph* [ti/abs] OR azinphos OR chlorethoxyphos OR chlorpyrifos OR coumaphos OR dichlorvos OR diazinon OR dicrotophos OR dimethoate OR disulfoton OR ethion OR fenitrothion OR fenthion OR isazaphos OR malathion OR methidathion OR parathion OR naled OR oxydemeton-methyl OR phorate OR phosmet OR pirimiphos-methyl OR sulfotepp OR temephos OR terbufos OR tetrachlorvinphos) AND (child* OR infan* OR toddler* OR birth*)

OR

(organophosph* [ti/abs] OR azinphos OR chlorethoxyphos OR chlorpyrifos OR coumaphos OR dichlorvos OR diazinon OR dicrotophos OR dimethoate OR disulfoton OR ethion OR fenitrothion OR fenthion OR isazaphos OR malathion OR methidathion OR parathion OR naled OR oxydemeton-methyl OR phorate OR phosmet OR pirimiphos-methyl OR sulfotepp OR temephos OR terbufos OR tetrachlorvinphos) AND (child* [ti/abs] OR infan* [ti/abs] OR toddler* [ti/abs] OR birth* [ti/abs])

OR

(organophosph* [ti/abs] OR dialkylphosphate* OR "dialkyl phosphate" OR "dialkyl phosphates" OR azinphos OR chlorethoxyphos OR chlorpyrifos OR coumaphos OR dichlorvos OR diazinon OR dicrotophos OR dimethoate OR disulfoton OR ethion OR fenitrothion OR fenthion OR isazaphos OR malathion OR methidathion OR parathion OR naled OR oxydemeton-methyl OR phorate OR phosmet OR pirimiphos-methyl OR sulfotepp OR temephos OR terbufos OR tetrachlorvinphos) AND (child* [ti/abs] OR infan* [ti/abs] OR toddler* [ti/abs] OR birth* [ti/abs] OR school* [ti/abs] OR adult* [ti/abs] OR women [ti/abs] OR men [ti/abs])

Exclusions:

- poisoning [ti]
- intoxic* [ti]
- lice [ti], louse [ti]
- malaria [ti]
- pediculosis, pediculus [ti]

- mouse, mice, rat, rats, pig, pigs [ti]
- cell, cells [ti]
- case report [notes]

The search looked for papers that mentioned individual OPs and/or biomarkers that also included terms such as "child," "toddler," "birth," "adult," "women," and "men." The original search yielded more than 10,000 papers, so proximity terms were used to limit to papers where the first set and second set of terms (specified by "AND") were close to one another. This yielded 992 papers. A few other relevant studies that the authors were aware were added. Additional exclusion terms were added to remove toxicity studies, case reports, and accidental poisoning

The abstracts for the 992 papers were reviewed for relevance. Of the 992 papers, 39 studies were determined to be relevant. One paper (Yolton et al., 2013) is included that pre-dates the EPA review but was missed (as acknowledged later by EPA). There are several other papers published in 2015 and 2016 that EPA discussed in the 2016 response (U.S. EPA, 2016) to comments on the 2015 OP review, but which were not included in the original review. These include Cartier et al. (2015), Rauh et al. (2015), Ranaan et al. (2015), Engel et al. (2015), Fielder et al. (2015), Harley et al. (2016), Stein et al. (2016), and Donauer et al. (2016).

Of the 39 studies, 31 included measures related to neurodevelopment. The 2015 EPA review included 38 studies, so the additional literature nearly doubles the number of available studies. Included among the 31 studies are a pooled analysis of the four largest cohorts in the U.S. (CHAMACOS, HOME, Mt. Sinai, and Columbia), additional studies from the large U.S. birth cohorts (e.g., Furlong et al. 2017a, Gunier et al., 2017; Donauer et al., 2016; Engel et al., 2016) and studies from large European cohorts (e.g., Jusko et al., 2019, van der Dries et al., 2018). Some studies are from China, which EPA did not emphasize in the last review because of the unknown mix of OPs compared to the U.S.

While a systematic review is needed before concluding anything about how the new studies may support or contradict the prior literature, there are number of notable studies that generally do not support EPA's findings:

- The Donauer et al. (2016) study examined maternal DAP exposure and childhood cognition from ages 1-5 in the Cincinnati-based Health Outcomes and Measures of the Environment Study (HOME Study). It found that "exposure to organophosphate pesticides during pregnancy was not associated with cognition during early childhood."

- The Engel et al. (2016) study is a pooled analysis of four U.S. cohorts that examines mental development indices at 2 years of age. The authors found limited evidence for

OP effects but also found significant heterogeneity across the four cohorts. This is the only pooled analysis and it includes four studies that measured the same health outcome at the same time.

- The Yolton et al. (2013) study examined maternal DAP exposure and infant neurobehavior at 5 weeks in the HOME. The authors found "no detrimental effects of gestational exposure to OPs on neurobehavioral outcomes among young infants."

- The Millenson et al. (2017) study with the HOME cohort examined the relationship of prenatal organophosphate insecticide biomarkers with reciprocal social, repetitive, and stereotypic behaviors in 8-year old children, and modification of this relationship by child *PON1* polymorphisms. It found that "prenatal urinary DAP concentrations were not associated with children's social behaviors; these associations were not modified by child *PON1* genotype."

- The van den Dries et al. (2018) study examined associations between prenatal OP pesticide exposure and neurodevelopmental outcomes such as Attention-Deficit Hyperactivity Disorder (ADHD) and autistic traits. The authors conclude "we did not observe associations with ADHD and autistic traits in children. These are important null observations because of the relatively high background DAP concentrations across pregnancy, the relatively large sample size, and the 10-year follow-up of the offspring."

- The Jusko et al. (2019) study examined maternal DAP exposures and IQ at age 6 in the large European cohort Generation R Study. It found that "Consistent evidence of an association between higher maternal urinary DAP concentrations and lower child IQ scores at 6 y of age was not observed."

The large size of the literature published since the EPA 2015 review shows that EPA needs to reopen the review and include the new and older studies in a systematic review.

Table 2. Summary of study design for studies identified in literature search

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Butler-Dawson 2016	Organophosphorus pesticide exposure and neurobehavioral performance in Latino children living in an orchard community	orchard community, Pacific Northwest (Washington/Oregon), USA	Prospective cohort	Latino children between the ages of 5 and 12	Two exposure measures were used to estimate children's pesticide exposure: parent's occupation (agricultural or nonagricultural) and organophosphate residues in home carpet dust samples (dust samples collected at Time 1 and Time 2 between 2008 and 2011).	Neurobehavioral data were collected at two time points (Time 1 and Time 2) using a battery of six computer-based tests from the Behavioral Assessment and Research System (BARS) and four individually administered tests
Carmichael 2016	Residential agricultural pesticide exposures and risks of selected birth defects among offspring in the San Joaquin Valley of California	San Joaquin Valley, California, USA	Retrospective case-control study	Mother-infant/fetus pairs; case infants had a medically confirmed congenital heart defect; controls infants are non-malformed live-born infants randomly selected from birth hospitals.	Exposure assigned utilizing the CEHTP Pesticide Linkage Tool application which incorporates California PUR data. Pounds of pesticides used during a relevant time window within a 500m radius of a geocoded point interesting polygons with the buffer.	8 congenital heart defect phenotypes (heterotaxia, tetralogy of Fallot, d-transposition of the great arteries, hypoplastic left heart syndrome, coarctation of the aorta, pulmonary valvestenosis, perimembranous ventricular septal defect (VSD), and atrial septal defect (ASD) secundum)
Cartier 2016	Organophosphate insecticide metabolites in prenatal and childhood urine samples and intelligence scores at 6 years of age: results from the mother-child PELAGIE cohort (France)	Brittany, France	Prospective birth cohort	231 mother-child pairs enrolled during the mothers pregnancy of child	Measured nonspecific dialkylphosphate metabolites (DAP) of OP in one maternal urine sample, collected before 19 weeks gestation, and in one urine sample collected from their 6-year-old children. Calculated DM, DE, and DAP.	Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) used to evaluate cognitive function (administered at age 6). Two scores were calculated with the age standardized using 6 subtest WISC-IV norms: 1) working memory score (Digit Span and Letter–Number Sequencing subtests), and 2) verbal comprehension score (Similarities, Vocabulary, and Comprehension subtests).

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Chang 2018	The interactions among organophosphate pesticide exposure, oxidative stress, and genetic polymorphisms of dopamine receptor D4 increase the risk of attention deficit/hyperactivity disorder in children.	Taipei City Hospital, Taiwan	Retrospective case-control study	Children 4–15 years in north Taiwan: 93 with ADHD and 112 controls (age-matched children who visited Taipei City Hospital for non-ADHD-related purposes).	Spot urine and oral swab specimen were collected; from urine 6 dialkyl phosphate (DAP) metabolites of OPs and Oxidative stress biomarkers and polymorphisms of the dopamine receptor D4 gene (DRD4) were considered as effect modifiers.	ADHD diagnosis and clinically assessed at least three times; ADHD identified in following the DSM-IV-TR; SNAP-IV questionnaire was used to assess control children's behavior at home and in the classroom by the reports of their parent(s) and teachers, respectively. Children with suspected ADHD symptoms were further evaluated by pediatricians or psychiatrists.
Dalsager 2018	Associations of maternal exposure to organophosphate and pyrethroid insecticides and the herbicide 2,4-D with birth outcomes and anogenital distance at 3 months in the Odense Child Cohort	Odense, Denmark	Prospective birth cohort	858 newly pregnant women (between 1st of January 2010 and 31 st of December 2012) and their index child	Pesticide metabolites 3-phenoxybenzoic acid (3-PBA), 3,5,6-trichloro-2-pyridinol (TCPY), 2,4-Dichlorophenoxyacetic acid (2,4-D) and dialkyl phosphates(DAPs) were measured in urine samples collected in gestational week 28	Gestational length, birth weight, head and abdominal circumference were obtained from birth records and anogenital distance (AGD) was measured at age three month
Dalsager 2019	Maternal urinary concentrations of pyrethroid and chloropyrifos metabolites and attention deficit hyperactivity disorder (ADHD) symptoms in 2-4-year old children from the Odense Child Cohort	Odense, Denmark	Prospective birth cohort	948 newly pregnant women (between 1st of January 2010 and 31 st of December 2012) and their index child	Urine samples collected in GW 28 analyzed for the specific metabolite of chloropyrifos/chloropyrifos-methyl, TCPY (3,5,6-trichloro-2-pyridinol)	At age 27 months, the families were invited to complete the Child Behavior Checklist for ages 1½-5 years (CBCL:1½-5). A score on the CBCL:1½-5 ADHD scale above the 90th percentile is a predictor of later ADHD diagnosis

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Donauer 2016	An observational study to evaluate associations between low-level gestational exposure to organophosphate pesticides and cognition during early childhood	Cincinnati, Ohio	Prospective birth cohort	327 pregnant women and their subsequent live-born infant pairs	Twice during pregnancy (16 and 26 weeks gestation) urinary concentrations of 6 common dialkylphosphates, nonspecific metabolites of organophosphate pesticides, were measured. Aggregate concentrations of diethylphosphates, dimethylphosphates, and total dialkylphosphates were calculated.	Bayley Scales of Infant Development, 2nd Edition-Mental and Psychomotor Developmental indices (administered at ages 1, 2, and 3 years), the Clinical Evaluation of Language Fundamentals-Preschool, 2nd Edition (at age 4), and the Wechsler Preschool and Primary Scale of Intelligence, 3rd Edition (at age 5)
Engel 2016	Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 Months: an analysis of four birth cohorts	Salinas Valley, California, USA; Cincinnati, Ohio, USA; Manhattan, New York, USA; Manhattan, New York, USA	4 prospective birth cohorts	4 cohorts of pregnant women of various race/ethnicity backgrounds and their corresponding offspring	Maternal prenatal urine samples used to computed site-specific and pooled estimates of the association of total dialkyl (ΣDAP), diethyl (ΣDEP), and dimethylphosphate (ΣDMP) metabolite concentrations Modification by children's center, race/ethnicity, and PON1 genotype examined	Bayley Scales of Infant Development, 2nd Edition (BSID-II) was administered to children by psychometricians to assess current developmental functioning and generates a Mental Development Index (MDI) and Psychomotor Developmental Index (PDI)

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Eskenazi 2014	Organophosphate pesticide exposure, PON1, and neurodevelopment in school-age children from the CHAMACOS study	Salinas Valley, Monterey County, California, USA	Prospective birth cohort	>=18 years pregnant women (and corresponding child), <20 weeks gestation, Spanish- or English-speaking, eligible for Medi-Cal, receiving prenatal care, and planning to deliver at Natividad Medical Center	6 DAP metabolites: 3 dimethyl(DM) phosphate metabolites (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate) and 3 diethyl (DE) phosphate metabolites (diethylphosphate, diethylthiophosphate, diethyldithiophosphate) measured twice in maternal urine at the time of prenatal interviews PON1 genotpye and enzyme activity [phenyl acetate (ARYase)and paraoxon (POase)] measured from maternal, cord, and child blood samples.	Performance on the Conners' Kiddie Continuous Performance Test (K-CPT) at 5-years and the Wechsler Intelligence Scale for Children (WISC-IV) art 7-years
Fergusson 2019	Organophosphate pesticide exposure in pregnancy in association with ultrasound and delivery measures of fetal growth	Rotterdam, Netherlands	Prospective birth cohort	784 Mother-child pairs residing in the study area with three urine specimens during pregnancy	Maternal concentrations of 6 dialkylphosphates (DAPs) were measured using gas chromatography coupled with tandem mass spectrometry in urine samples collected at <18 weeks, 18-25 weeks, and >25 weeks of gestation; from this was created a subject-specific average to estimate OP exposure (total DMPs, DEPs, and DAPs)	Ultrasound measures of head circumference, femur length, and estimated fetal weight from middle and late pregnancy and delivery measures were converted to standard deviation scores.

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Fiedler 2015	Neurobehavioral effects of exposure to organophosphates and pyrethroid pesticides among Thai children	Rice and aquaculture farming regions outside of Bangkok, Thailand	Prospective cohort (cross-sectional analysis)	44, 6–8 year old, healthy male and female Thai children randomly selected from 200 volunteers recruited from rice (N = 25) and aquaculture farming (N = 29)	Capture exposure during the rainy or high pesticide use (HIGHUSE) and the dry or low pesticide (LOWUSE) use seasons. Participants completed Session II (HIGHUSE) and III (LOWUSE) testing sessions 6 months and one year after the initial testing session. Also, urine specimens collected at first session. Six DAP metabolites estimated and summed concentration of metabolites: DAP, DEAP, and DMAP as well as TCPy.	Behavioral Assessment and Research System (BARS), has been adapted and augmented for use with children, age 5 and above. Battery of several test examined: Latency of response (SDT,MTS,CPT), Accuracy of response (MTS,CPT), Motor speed (TAP,DAT,PEG), Learning (OMT,VMI,DST):
Fratric 2017	Cryptorchidism and pesticides: Is there a connection?	(probably) Novi Sad, Serbia	Cross-sectional case-control study	60 women (30 mothers of infants with cryptorchidism, 30 control mothers of infants without cryptorchidism); newborns (born 38 to 42 weeks gestation); mothers 18 to 45 years	Urine samples were taken on 3rd postpartum day; gas chromatography with flame photometric detection was used to analyze dimethyl phosphate in urine; concentration were creatinine adjusted	Clinical diagnosis of cryptorchidism was made via direct clinical examination by a pediatric urologist
Furlong 2017b	Prenatal exposure to organophosphorus pesticides and childhood neurodevelopmental phenotypes	New York City, New York, USA	Prospective birth cohort	Primiparous mothers with singleton pregnancies that delivered at the Mount Sinai Hospital between May 1998 and July 2001	Six dialkylphosphate metabolites, including three dimethylphosphate (DMP) and three diethylphosphate (DEP) metabolites, were analyzed in two batches between 2002 and 2003 at the Centers for Disease Control and Prevention (CDC)	Measured children's executive functioning and behavior at the 4, 6, and 7–9 year visits using parent report measures, and IQ at the 6 and 7–9 year visits using performance-based measures.

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Gonzalez-Alzaga 2015	Pre- and postnatal exposures to pesticides and neurodevelopmental effects in children living in agricultural communities from South-Eastern Spain	El Poniente, Spain	Retrospective /prospective cohort	305 children aged 6–11 years randomly selected from public schools of the study area	OP pesticides assessed by biomonitoring urinary levels of metabolites of these compounds at 2 time points of the same crop season, representing low and high pesticide use (January–February and October, 2010, respectively). Total DAPs, DMs, and DEs estimated. Both prenatal and postnatal residential exposure to pesticides was estimated by developing a geographical information system (GIS) technology-based index that integrated distance-weighted measure of agricultural surface, time-series of crop areas per municipality and year, and land-use maps.	Neuropsychological performance was evaluated with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV). Full-scale IQ, and four subdomains (Verbal comprehension, Perceptual reasoning, Working memory, Processing speed) were calculated.
Gunier 2017	Prenatal residential proximity to agricultural pesticide use and IQ in 7-year-old children	Salinas Valley, Monterey County, California, USA	Prospective birth cohort	>=18 years pregnant women (and corresponding child), <20 weeks gestation, Spanish- or English-speaking, eligible for Medi-Cal, receiving prenatal care, and planning to deliver at Natividad Medical Center	An SD increase in toxicity-weighted OP pesticide use within 1 km of maternal residence during pregnancy a SD increase in neurotoxic pesticide use within 1 km of maternal residence during pregnancy	Full scale IQ score and scores from four subdomain (Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed) based on performance on the Wechsler Intelligence Scale for Children (WISC-IV) at 7-years

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Guo 2019	Associations of prenatal and childhood chloropyrifos exposure with Neurodevelopment of 3-year-old children.	Sheyang county, Jiangsu province, China	Prospective birth cohort	377 pregnant women from an agricultural region and their children were followed up from birth to age 3	Urine sample collected from each mother prior to delivery; children's urinary samples were collected at maternal and child care center when visiting for neurodevelopmental assessment; urinary 3,5,6-Trichloro-2-pyridinol (TCPy), a specific metabolite of CPF, was quantified using large-volume-injection gas chromatography tandem mass spectrometry	Neurodevelopment of children assessed by trained pediatrician using the Gesell Developmental Schedules, and developmental quotients calculated for four domains of neurobehavioural functions (motor, adaptive, language, and social functions)
Harley 2016	Prenatal exposure to organophosphorous pesticides and fetal growth: pooled results from four longitudinal birth cohort studies	Salinas Valley, California, USA; Cincinnati, Ohio, USA; Manhattan, New York, USA; Manhattan, New York, USA	Prospective cohort	4 cohorts of pregnant women of various race/ethnicity backgrounds and their corresponding offspring	Measured nonspecific dialkylphosphate metabolites (DAP) of OP in one or two maternal urine samples	Birth weight, birth length, and head circumference
Huang 2017	Concurrent exposures to nonylphenol, bisphenol A, phthalates, and organophosphate pesticides on birth outcomes: A cohort study in Taipei, Taiwan	Cathay General Hospital, Taipei, Taiwan.	Prospective birth cohort	162 women, 18–45 years, <13 weeks pregnant with detection of fetal heart beat at the 1st prenatal visit, and their corresponding newborns	3 spot urine samples at approximately 11 weeks and 26 weeks gestation and at delivery; 6 OP pesticide metabolites, including three metabolites of DMPs (DMP, DMTP, and DMDTP) and three metabolites of DEPs (DEP, DETP, and DEDTP), were analyzed using isotope dilution GC/MS method	Recorded neonatal birth weight (g), length (cm), and head and chest circumference (cm) around the time of delivery

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Jaacks 2019	Association of prenatal pesticide exposures with adverse pregnancy outcomes and stunting in rural Bangladesh	Bangladesh	Prospective birth cohort	289 pregnant women (aged 18–40 years) living in rural Bangladesh and the index child at birth and approximately 1 and 2 years of age.	Eight pesticide biomarkers were quantified in urine [four organophosphate insecticide metabolites, 3,5,6-trichloro-2-pyridinol (TCPY, a metabolite of chloropyrifos and chloropyrifos methyl), 4-nitrophenol (a metabolite of parathion and methyl parathion), malathion dicarboxylic acid (MDA, a malathion metabolite), and 2-isopropyl-4-methyl-6-hydroxypyrimidine (IMPY, a diazinon metabolite)]	Gestational age by ultrasound at enrollment anthropometry measurements were conducted on the index child at birth and approximately 1 and 2 years of age.
Jusko 2019	Organophosphate pesticide metabolite concentrations in urine during pregnancy and offspring nonverbal IQ at age 6 years	Rotterdam, Netherlands	Prospective birth cohort	Mother-child pairs residing in the study area with three urine specimens during pregnancy	Maternal urinary concentrations of 6 dialkylphosphates (DAPs), collected at <18, 18–25, and >25 weeks of gestation Examined potential effect measure modification by PON1 gene (from cord blood sample)	nonverbal IQ measured at age 6 using the Mosaics and Categories subtests from the Snijders-Oomen Nonverbal Intelligence Test–Revised
Kongtip 2017	The impact of prenatal organophosphate pesticide exposures on Thai infant neurodevelopment	Amnartcharoen, Karnjanaburi, and Nakorn Sawan, Thailand	Prospective birth cohort	50 pregnant women aged 20 to 35 years old and their infants who received care at one of 3 hospitals. Only children born at full term with normal labor were eligible for postnatal follow-up.	Spot urine samples were collected at 28 weeks gestation and analyzed by gas chromatography-mass spectrometry to determine maternal metabolite levels of OP pesticides including dimethyl phosphate (DMP); total DEP (diethyl phosphate (DEP), diethyl thiophosphate (DETP), and diethyl dithiophosphate (DEDTP), and total DAP (the sum of all metabolite levels)	At 5 months of age, infant development was evaluated using the Bayley Scales of Infant and Toddler Development-III (Bayley-III).

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Liu 2016	Adverse associations of both prenatal and postnatal exposure to organophosphorous pesticides with infant neurodevelopment in an agricultural area of Jiangsu Province, China: a cohort study	Sheyang county, Jiangsu province, China	Prospective birth cohort	310 healthy pregnant women who gave birth at local maternity hospitals without serious chronic diseases	Measured dimethyl phosphate (DMs), diethyl phosphate (DEs), and total dialkyl phosphate (DAPs) metabolites in maternal urine collected before delivery and in urinary samples of their children aged 2 years	Neurodevelopment of children at age 2 years using the Gesell Developmental Schedules, and developmental quotients calculated for four domains of neurobehavioural functions (motor, adaptive, language, and social functions)
Millenson 2017	Urinary organophosphate insecticide metabolite concentrations during pregnancy and children's interpersonal, communication, repetitive, and stereotypic behaviors at 8 years of age: The home study	Cincinnati, Ohio	Prospective birth cohort	224 pregnant women and their subsequent live-born infant pairs	Twice during pregnancy (16 and 26 weeks gestation) urinary concentrations of 6 common dialkylphosphates, nonspecific metabolites of organophosphate pesticides, were measured. Aggregate concentrations of diethylphosphates, dimethylphosphates, and total dialkylphosphates were calculated.	Administered the Social Responsiveness Scale (SRS), a continuous measure of various dimensions of interpersonal behavior, communication, and repetitive/stereotypic behaviors (administered at 8 yr).
Philippat 2018	Prenatal exposure to organophosphate pesticides and risk of autism spectrum disorders and other non-typical development at 3 years in a high-risk cohort	Davis, California, USA	Prospective birth cohort	203 mother-child pairs of the ongoing MARBLES mother-child cohort, which enrolls mothers who are either pregnant or planning a pregnancy and whose expected child has an elevated risk to develop ASD	7 metabolites of OPs were assessed in repeated urine samples collected during pregnancy	at 36 mo, children were assessed with instruments measuring cognitive function and adaptive behaviors, and with two gold-standard diagnostic instruments for ASD: the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Rauh 2016	Prenatal exposure to the organophosphate pesticide chloropyrifos and childhood tremor	New York City, New York, USA	Prospective birth cohort	263 mothers/child-pairs; children were inner-city minorities, approximately 11-14 yrs old	Prenatal exposure to CPF was measured in umbilical cord blood and in maternal blood within 2 days of delivery. Chloropyrifos levels were categorized into 4 groups: non-detectable levels and 3 tertiles in the detectable range.	At approximately 11 years of age during a europsychological assessment, children were asked to draw Archimedes spirals. These were rated with a spiral score relating by a senior neurologist specializing in movement disorders. Evidence of tremor was based upon spiral score (>=1)
Sagiv 2018	Prenatal organophosphate pesticide exposure and traits related to autism spectrum disorders in a population living in proximity to agriculture	Salinas Valley, Monterey County, California, USA	Prospective birth cohort	>=18 years pregnant women (and corresponding child), <20 weeks gestation, Spanish- or English-speaking, eligible for Medi-Cal, receiving prenatal care, and planning to deliver at Natividad Medical Center	OP exposure during pregnancy with measurements of dialkylphosphates (DAP) metabolites in urine (DAPs, DEs, DMs), and residential proximity to OP (kg within 1 km) use during pregnancy using California's Pesticide Use Reporting (PUR) data	ASD-related traits measured through reported by parents (Social Responsiveness Scale, Version2 at age 14y; Behavioral Assessment Scale for Children, Version 2 (BASC-2) at ages 7, 10½, and 14y) and teachers (BASC-2 at ages 7) as well as the child's performance on tests that evaluate the ability to use facial expressions to recognize the mental state of others (Evaluación Neuropsicológica Infantil (ENI) Facial Expression Recognition Test at age 9y and the NEPSY-II Affect Recognition subtest at age 12y).

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Schmidt 2017	Combined prenatal pesticide exposure and Folic Acid intake in relation to autism spectrum disorder	California, USA	Retrospective case-control study	California children born from 2000–2007 enrolled in CHARGE at age 2-5 yr with clinically confirmed ASD (n=296) or typical development (n=220)	Household pesticide exposure (question: "Did you or anyone in your household use [consumer pesticide item]?") Commercial pesticide exposure based upon California Pesticide use reports (PURs) and proximity of residence to application of pesticide Occupational pesticide exposure based upon parental occupation information Organophosphates collectively and Chloropyrifos specifically where examined. Modification by folic acid investigated	Clinically confirmed Autism spectrum disorder (ASD)
Shaw 2014	Early pregnancy agricultural pesticide exposures and risk of gastroschisis among offspring in the San Joaquin Valley of California	San Joaquin Valley, California, USA	Retrospective case-control study	Mother-infant/fetus pairs; case infants had a medically confirmed birth defect; controls infants are non-malformed live-born infants randomly selected from birth hospitals.	Exposure assigned utilizing the CEHTP Pesticide Linkage Tool application which incorporates California PUR data. Pounds of pesticides used during a relevant time window within a 500m radius of a geocoded point interesting polygons with the buffer.	4 types of clinically confirmed birth defect (anencephaly, spina bifida, cleft lip with or without cleft palate (CLP), or cleft palate only)

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Silver 2017	Prenatal naled and chlorpyrifos exposure is associated with deficits in infant motor function in a cohort of Chinese infants	Fuyang (mostly rural county), Zhejiang, China	Prospective birth cohort	237 healthy, pregnant women and their singleton infants with sufficient volume of cord blood for pesticide analysis.	30 OPs were measured in umbilical cord blood using gas chromatography tandem mass spectrometry	Motor function was assessed at 6 wks and 9 mo using Peabody Developmental Motor Scales 2nd edition (PDMS-2). Outcomes included subtest scores: reflexes, stationary, locomotion, grasping, visual-motor integration (V-M), composite scores: gross (GM), fine (FM), total motor (TM), and standardized motor quotients: gross (GMQ), fine (FMQ), total motor (TMQ).
Silver 2018	Prenatal organophosphate insecticide exposure and infant sensory function	Fuyang (mostly rural county), Zhejiang, China	Prospective birth cohort	237 healthy, pregnant women and their singleton infants with sufficient volume of cord blood for pesticide analysis.	30 OPs were measured in umbilical cord blood using gas chromatography tandem mass spectrometry	Outcomes included visual acuity (VA) score, auditory brainstem response (ABR) wave V latency and central conduction time, and head circumference (HC). Infant development was assessed at three follow-up visits around 6 wks, 9 mo, 18 mo.
Stein 2016	Early childhood adversity potentiates the adverse association between prenatal organophosphate pesticide exposure and child IQ: The CHAMACOS cohort	Salinas Valley, Monterey County, California, USA	Prospective birth cohort	>=18 years pregnant women (and corresponding child), <20 weeks gestation, Spanish- or English-speaking, eligible for Medi-Cal, receiving prenatal care, and planning to deliver at Natividad Medical Center	Mean maternal prenatal urinary total DAP concentration (nmol/L) (averaged from urine sampled taken at 13 weeks and 26 weeks gestation) High/low standardized adversity score	Full scale IQ score and scores from four subdomain (Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed) based on performance on the Wechsler Intelligence Scale for Children (WISC-IV) at 7-years

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
van den Dries 2019	Organophosphate pesticide metabolite concentrations in urine during pregnancy and offspring attention-deficit hyperactivity disorder and autistic traits	Rotterdam, Netherlands	Prospective birth cohort	784 Mother-child pairs residing in the study area with three urine specimens during pregnancy	Maternal concentrations of 6 dialkylphosphates (DAPs) were measured using gas chromatography coupled with tandem mass spectrometry in urine samples collected at <18 weeks, 18-25 weeks, and >25 weeks of gestation	ADHD traits were measured at ages 3, 6, and 10 years using the Child Behavior Checklist (CBCL) Autistic traits were measured at age 6 years using the Social Responsiveness Scale (SRS)
Wang 2016	Urinary metabolites of organophosphate and pyrethroid pesticides and neurobehavioral effects in Chinese children	Nanjing, China.	Cross-sectional study	406 randomly selected children aged 3−6 years from three kindergartens in Nanjing (including urban and rural areas), with no reported diseases and in good health	Morning urine samples collected by parents from children; from the samples 3,5,6-trichloropyridinol (TCP), a specific metabolite of chloropyrifos, was measured	Chinese Binet test, arithmetic test, picture completion test, maze test, and cancellation test scores calculated (arithmetic test, picture completion test, and maze test obtained from the Wechsler preschool and primary scale of intelligence)
Wang 2017	Prenatal and postnatal exposure to organophosphate pesticides and childhood neurodevelopment in Shandong, China	Laizhou Wan (Bay) of the Bohai Sea, Shandong, China	Prospective birth cohort	March 2011 to December 2013, 436 women were recruited when admitted in labor	Diethylphosphate (DE), dimethylphosphate (DM), and total dialkylphosphate (DAP) metabolites in maternal (prenatal at admission for labor) and child urine at 12 and 24 months of age	Gesell Developmental Schedules for 0- to 3-year-old children to the 12-month-old infants and 24-month-old children in this cohort. In each of the four domains (social, language, adaptive, and motor), a developmental quotient (DQ) was assigned to each child.

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Wang 2019	Prenatal exposure to organophosphate pesticides, maternal paraoxonase 1 genotype, and childhood neurodevelopment at 24 months of age in Shandong, China	Laizhou Wan (Bay) of the Bohai Sea, Shandong, China	Prospective birth cohort	March 2011 to December 2013, 436 women were recruited when admitted in labor	Six urinary DAP metabolites were measured by using gas chromatography-mass spectrometry (GC-MS): three dimethyl (DM) phosphate metabolites, dimethylthiophosphate (DMTP), dimethylphosphate (DMP), dimethyldithiophosphate (DMDTP), and three diethyl (DE) phosphate metabolites, diethylthiophosphate (DETP), diethylphosphate (DEP), and diethyldithiophosphate (DEDTP) in maternal (prenatal at admission for labor) urine. Modification by PON1–108C/Tand PON1192Q/R genotypes investigated	Gesell Developmental Schedules for 0- to 3-year-old children to 24-month-old children in this cohort. In five domains (social, language, adaptive, fine motor and gross motor), a developmental quotient (DQ) was assigned to each child.
Woskie 2017	A pilot study of maternal exposure to organophosphate pesticides and newborn neurodevelopment in Thailand	Amnartcharoen, Karnjanaburi, and Nakorn Sawan, Thailand	Prospective birth cohort	pregnant women recruited during the 28th week of pregnancy from three government provincial hospitals	Pesticide exposure examined as: (1) a dichotomous variable where the mother was defined as an agricultural worker, or not; and (2) from maternal urinary specimen, as the individual OP metabolite concentration or as the total of all DEP metabolite levels for each woman	Within 3 days of birth, neurobehavioral testing conducted using the Brazelton Neonatal Behavioral Assessment Scale (NBAS) with 7 sub-assessment cluster scores (Habituation, Orientation, Motor performance, Range of state, Regulation of state, Autonomic stability, Number of abnormal reflexes)

Author	Title	Location	Study Design	Study Subjects	Exposure Assessment	Outcome Assessment
Yang 2014	Residential agricultural pesticide exposures and risk of neural tube defects and orofacial clefts among offspring in the San Joaquin Valley of California	San Joaquin Valley, California, USA	Retrospective case-control study	Mother-infant/fetus pairs; case infants had a medically confirmed birth defect; controls infants are non-malformed live-born infants randomly selected from birth hospitals.	Exposure assigned utilizing the CEHTP Pesticide Linkage Tool application which incorporates California PUR data. Pounds of pesticides used during a relevant time window within a 500m radius of a geocoded point interesting polygons with the buffer.	4 types of clinically confirmed birth defect (anencephaly, spina bifida, cleft lip with or without cleft palate (CLP), or cleft palate only)
Yolton 2013	Impact of low-level gestational exposure to organophosphate pesticides on neurobehavior in early infancy: a prospective study	Cincinnati, Ohio	Prospective birth cohort	350 mother/infant pairs, singleton births, living in housing built before 1978. <19 weeks at enrollment	Measured 6 common dialkylphosphate metabolites of OP pesticides in maternal urine, at 2 times during pregnancy (16 wk & 26 wk gestation), then calculated aggregate concentrations of diethylphosphate, dimethylphosphate, and total dialkyphosphate metabolites.	Measured infant neurobehavior at about 5 wks of age at a home visit using the NICU Network Neurobehavioral Scale (NNNS), a comprehensive assessment of neurobehavior in young infants.
Yu 2016	Increased risk of attention-deficit/hyperactivity disorder associated with exposure to organophosphate pesticide in Taiwanese children	Taipei, Taiwan	Retrospective case-control	97 doctor-diagnosed ADHD cases and 110 non-ADHD controls who were Taiwanese children, ages 4–15, outpatient of Taipei City Hospital	Urine samples from children were used to calculate six DAP metabolites (DMP, DEP, DMTP, DMDTP, DETP, and DEDTP)	clinically-diagnosed ADHD

Conclusions

The U.S. EPA 2015 review of OP epidemiologic studies related to neurodevelopment and birth outcomes performed a systematic review prior to guidance issued on systematic review the following year. As a result, there are some key differences in EPA's OP review compared to a later review completed for pyrethroids in 2019. In fact, in some cases, the same or similar studies were rated differently in the OP and pyrethroid reviews. The primary reason for the different ratings was the criteria used to evaluate the exposure assessment.

Additionally, a literature search yielded 39 additional studies published since the 2015 OP review. Of these, 31 studies were related to neurodevelopment effects, which was the basis for reinstating the FQPA factor on all organophosphates. The 2015 OP review included 38 studies related to neurodevelopment, so the new literature is nearly as large as the original literature.

It is recommended that EPA revisit the Literature Review in light of the points made in this submission, the Agency's own 2016 guidance and additional data that has been provided to the Agency regarding organophosphates.

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Message

From: Laura McConnell [laura.mcconnell@bayer.com]
Sent: 10/26/2017 2:41:37 PM
To: danesha_carley@ncsu.edu; ksolomon@uoguelph.ca; giscott0@mailbox.sc.edu; jbdubois@ncsu.edu; Ex. 6 PP – personal email; Catherine LePrevost [celeprev@ncsu.edu]; armbrust@lsu.edu; Costello, Kevin [Costello.Kevin@epa.gov]; marie.delorenzo@noaa.gov; teung.chin@ars.usda.gov; David.Knaebel@ARS.USDA.GOV; kernm@waterborne-env.com; jgiddings@complianceservices.com; ted.valenti@syngenta.com; spencer.mortensen@basf.com; CTerry@dow.com; steven.l.levine@monsanto.com; Scott.Jackson@valent.com; cmorgan@deltacouncil.org; alan.samel@dupont.com; David Fischer [david.fischer@bayer.com]; Tamar Schlekat [tamar.schlekat@setac.org]; Odenkirchen, Edward [Odenkirchen.Edward@epa.gov]; Waleko, Garland [Waleko.Garland@epa.gov]; Cobb, George [George_Cobb@baylor.edu]; gcope@ncsu.edu; LAbbott@oce.usda.gov; David Monks [dwm@ncsu.edu]
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Subject: Presentations from NC State Workshop
Attachments: Solomon_2017-10-23S-WoE-NCS-Wkshop_2.pdf; Mitchell Pyrethroid Workshop_2.pdf; Giddings presentation 10-20-17_2.pdf; Costello_OPP presentation for NCSU 101817_2.pdf; Introtalk_McConnell_3.pdf

Dear all,
As promised, here are pdfs of the presentations from the first morning.
Best regards,
Laura

Laura McConnell
Principal Scientist, Environmental Chemistry

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Overview of US EPA Risk Assessment and Risk Management Approach to the Utilization of Higher Tier Studies

Kevin Costello, Edward Odenkirchen and Garland Waleko

USEPA Office of Pesticide Programs

October 23, 2017

Standard Ecological Risk Assessments

- The Agency calls in a standard set of environmental fate and ecotoxicity data for every pesticide
- The fate data are used to characterize and predict exposure values
- Estimated exposure is compared to toxicity endpoints from ecotox data
  - Exposure above a level of concern (LOC) indicates a potential concern warranting further analysis
  - Endpoints of concern are survival, growth and reproduction
- Non-guideline data (including open literature) are considered either quantitatively or in risk characterization

Goals of Tiered Risk Assessments

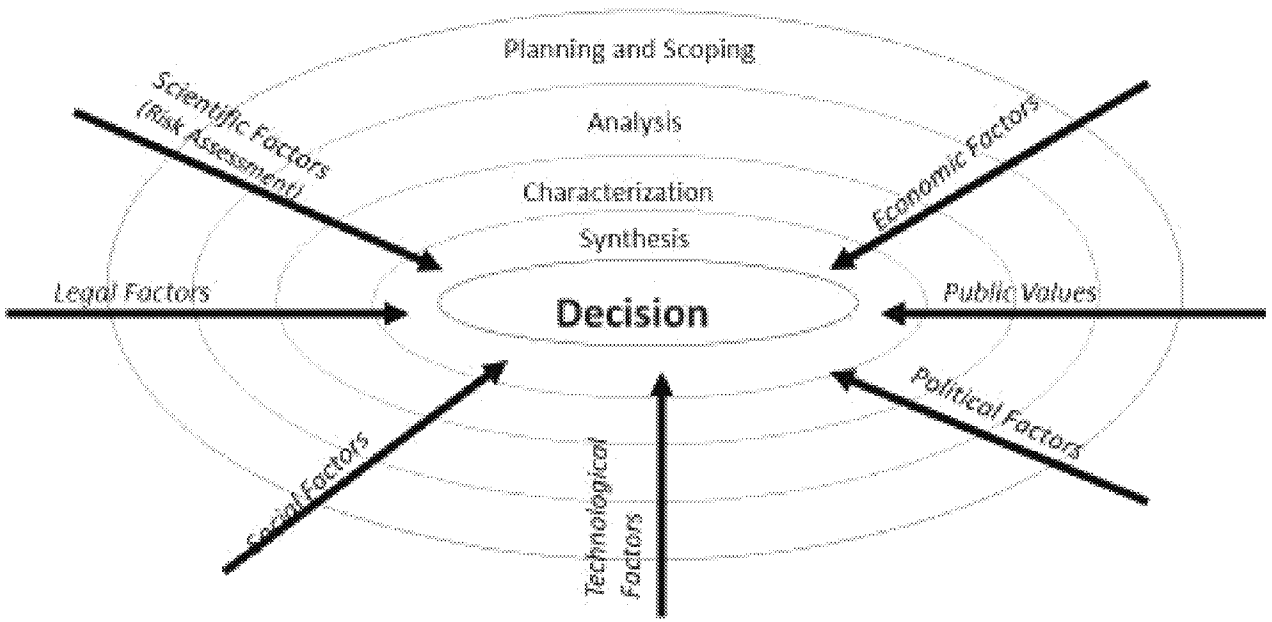
Implement a refined assessment process that

- Addresses a broad spectrum of effects
- Reflects more realistic use scenarios and field conditions
- Incorporates probabilistic tools and methods
- Is designed to rely on existing data requirements for registration at lower tiers
- Focuses additional data requirements in upper tiers for reducing uncertainty

Risk Assessments in the Risk Management Process

- Risk assessments are one factor considered when making a risk management decision
- Public comments factor into the decision, and receive responses
- Additional refinements or higher tier studies can be considered or called in if they are crucial to making the decision.

Risk Management Framework



Role of the Risk Manager

- Responsible for leading OPP's registration or reevaluation process
- Risk managers must:
  - Consider the results of the risk assessments
  - Have an understanding of the benefits of a pesticide, as well as alternative pesticides that are already registered
  - Develop measures needed to mitigate any identified risks
  - Negotiate modifications to the product or labeling that must be made to mitigate risk

Role of Benefits Assessments

- Ecological & Worker: FIFRA requires consideration of both risks & benefits
  - Established methodologies for estimating costs for growers and for evaluating alternatives
  - If the risk/benefit balance is clear, decision may not need extensive analysis of benefits
- Dietary: FFDCA does not allow for risk/benefit balancing.
  - However, Agency looks for best solutions that take benefits into account

When does the Agency Use Higher Tier Studies?

- When the standard risk assessment, in the context of other factors, is not enough to answer the questions at hand
- When potential risks and benefits both appear to be great
- When the expenditure of resources is warranted by the decision to be made

Tier II Honey Bee Toxicity Studies (semi-field)

- Standard risk assessment could not address questions about the role of pesticides in honey bee declines
  - Available studies addressed acute toxicity to adult bees, but not to larva or colonies
  - Protection of bees an important public value, and economically important
- Appropriately vulnerable exposure scenario was used and agreed upon by the Agency/international community (e.g., bees exposed in tunnels or long-term feeding of colonies).
- Risk assessment/protection goals clearly defined (assessment endpoint = colony strength/survival measurement endpoint = overwintering success, sustained impacts on colony strength/fitness)
- Study outcomes related directly to risk assessment process (e.g., used to interpret residues in pollen/nectar)
- Single population (not entire community)

Petitions

- Plaintiffs sue for tolerance revocations, claiming failure to meet safety standards under FFDCA
- Chemicals subject to these petitions generally higher risk and higher benefit
- Risk assessments for petitions are done on court-order deadlines which can be extended in court, but not missed
- Often require development and use of "higher tier" models and approaches.

PBPK Modeling in Risk Assessment

- State-of-the-art science developed in conjunction with registrants
- PBPK modelling is a scientifically sound and robust approach to estimating the internal dose of a chemical at a target site and as a means to evaluate and describe the uncertainty in risk assessments.
- PBPK models consist of a series of mathematical representations of biological tissues and physiological processes in the body

PBPK Modeling in Risk Assessment

- Model applications in risk assessments:
  - interspecies extrapolation, intraspecies extrapolation, route-to-route extrapolation, estimation of response from varying exposure conditions, and high-to-low dose extrapolation
- Very resource intensive, has required multiple rounds of peer review

How the Agency Uses Voluntarily Submitted Studies

- The best-case scenario involves collaboration on the design of a study meant to answer a specific question
- Many high-quality studies are submitted without this kind of planning
  - For the pyrethroids, there are hundreds of such studies
  - The utility of these studies for the risk management decision is determined after they are completed and submitted

Types of Voluntarily Submitted Studies

- Some studies might refine quantitative risk assessment
  - Studies can refine model inputs for risk assessment
  - Studies can be used to develop new models, but this is costly
  - Studies which expand risk assessment from the lab to the field
- Some studies provide lines of evidence for the risk management decision
  - Studies can inform potential mitigation
  - Studies can present potential risk using less conservative scenarios

Studies which refine inputs to models

- Calculation of partitioning coefficients for free dissolved pyrethroids instead of those for whole water (including suspended sediments)
  - Resulting modeled acute concentrations were up to 10 times lower
  - Predicted risks to aquatic invertebrates remain
- Studies measuring removal of pyrethroids during wastewater treatment
  - Bench scale water treatment removal study (designed in collaboration with OPP)
  - Wastewater monitoring performed before and after treatment

Studies which inform potential mitigation

- Source evaluation of residential uses in surface water runoff – The PWG Pathway Identification Study in which residential sprays were simulated by application to walls, lawns and driveways set up to receive a known amount of "rainfall."
- Runoff of material applied to impermeable surfaces was much greater than that applied to grass or walls near grass
- Results of this and other runoff studies were described in the risk assessment, but not applied quantitatively
- The Pathway Identification Study informed mitigation that reduced the area on a structure that could be treated with pyrethroids

Studies which provide lines of evidence from the field

- Mesocosm studies can show population or community effects from exposure to pesticides
- May show that certain affected populations might be adversely effected temporarily, only to recover later.
- Some species might not recover, but be replaced by other similar species

Mesocosms, continued

- Historically, mesocosm data conducted under FIFRA have been difficult to interpret
  - Confounding factors contributing to uncertainty in results
  - Study designs not appropriately focused (trying to assess too many endpoints/attributes with finite resources, such that none are done with the level of rigor needed
  - Regulatory assessment endpoint not clearly defined (what level of impact and duration of recovery is "acceptable"?)
- Mesocosm may not align with risk assessment goals
  - E.g: Many mesocosm studies evaluate short term, single pulse exposure; difficult to extrapolate to national-level risk assessment goals

Use of mesocosms for atrazine

- Data from many mesocosms were used quantitatively to develop a water concentration LOC for atrazine reregistration decision
  - Endpoint of concern based on primary productivity
  - Several years of analysis in preparation for the 2003 RED
  - Revised twice in response to 2007 and 2009 Science Advisory Panels
- Original tool relied on 35 atrazine mesocosms
- After 2009, 46 mesocosms from a set of 86 were employed
- Very resource intensive, very data intensive
- The complexity of the decision must merit the resource expenditure

Conventional Registration Review Status

- The resources OPP can spend on individual registration review cases is tied to those needed for the program as a whole
- By Oct 1st, 2022, OPP must complete:
  - ~184 draft risk assessments (40% remaining)
  - ~273 proposed interim decisions (60% remaining)
  - ~295 final or interim decisions (64% remaining)
- Each risk assessment and proposed decision requires peer review, and opens a public comment period
- If mitigation is needed, time is required for negotiations

Conclusions

- "Higher tier" studies work best when designed with the Agency to answer specific questions tied to risk management goals
- Resource constraints limit the number of voluntarily submitted studies OPP can fully review
- However, the Agency does use "higher tier" studies in many risk assessments
- Some studies directly apply to our quantitative risk assessments, and some provide lines of evidence for risk management decisions
- The level of effort must conform to the complexity of a decision

Using higher tier data in aquatic risk assessment of pyrethroids for FIFRA Registration Review

Jeffrey Giddings, *Compliance Services International*
On behalf of the Pyrethroid Working Group

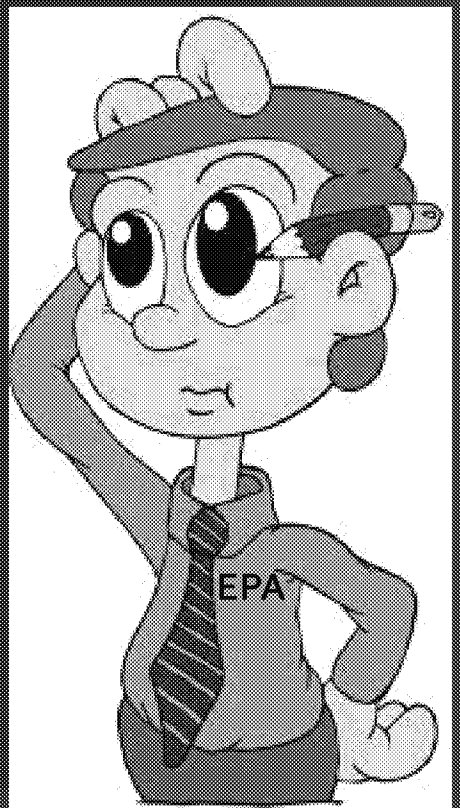
2017 Workshop on Innovation and Regulation in Agriculture
October 23-24, 2017
Raleigh, NC

Why consider higher tier data?

- A screening level assessment is a useful first step.
  - Identifies taxa and uses where risk is minimal, no further analysis needed
  - Prioritizes taxa and uses for further analysis
  - Supports protective regulatory decisions when data are limited
- But a screening level assessment goes only partway toward definitive answers to most risk assessment questions.
- Higher tier data support a more complete and accurate understanding of potential ecological effects.
- Because pyrethroids are a data-rich class of pesticides, PWG's assessment incorporated a variety of available higher tier data.

Higher-tier data used in PWG's risk assessment

- Species Sensitivity Distributions (SSDs)
- Refined exposure modeling
- Bioavailability calculations (using best-available K_{OC} values)
- Pathway ID study (runoff from outdoor residential uses)
- Landscape analysis
- Residue monitoring data
- Exposure uncertainty analysis
- Mesocosms
- Bioassessments



What am I supposed to do with these data?

- Protection goals need to be defined
  - Individual, population, community level
  - Magnitude and likelihood of effect
- What is the risk assessment question?
- How does the screening level address the question?
- What questions and uncertainties remain at the conclusion of the screening-level assessment? [updated Problem Formulation]
- How can higher tier data be used to address the remaining questions and uncertainties?

RQ < LOC is not a protection goal

Species Sensitivity Distributions (SSDs)

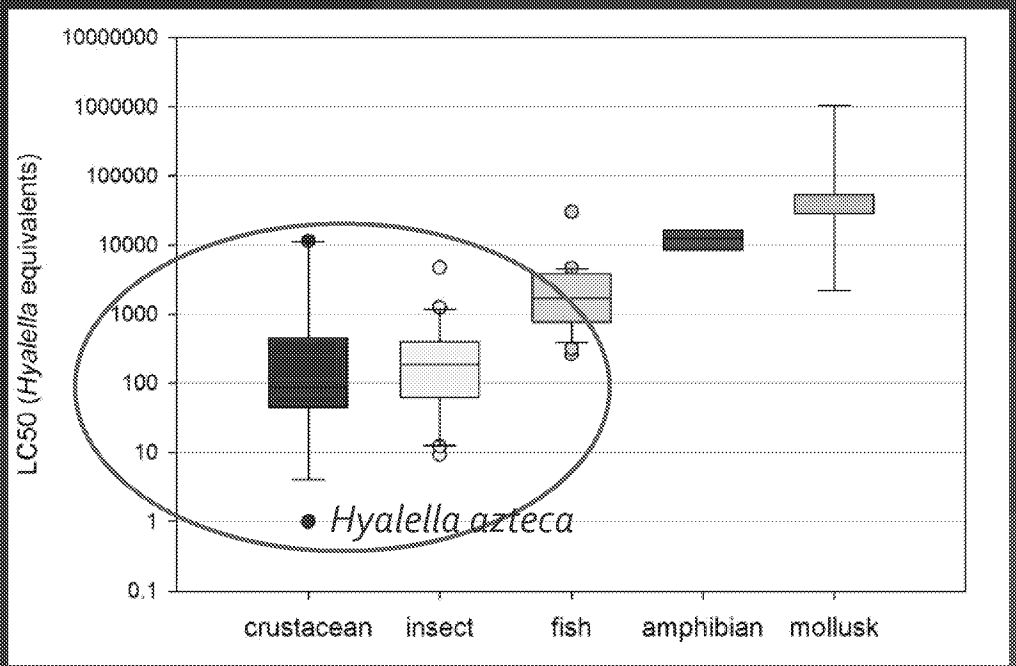
- Risk assessment question: What are the potential effects of the pesticide on populations and ecological communities?
- Screening-level approach: Consider the most sensitive tested species, apply a safety factor, infer a "safe" exposure concentration
  - A prudent approach when data are limited
  - Highly likely to encompass the most sensitive species in any habitat
  - Vulnerable to the influence of outlying toxicity data

Species Sensitivity Distributions (SSDs)

- Remaining questions and uncertainties
  - How does the pesticide affect the range of species in a community (not only the most sensitive species)?
  - What is the likelihood of an effect on a particular untested species?
- Higher-tier approach: Consider data for all tested species
  - Highly informative when data are plentiful (many older pesticides)
    - Pyrethroid toxicity data for >300 species
  - SSD analysis addresses the risk questions probabilistically (magnitude and likelihood of effect)

Crustaceans and insects (arthropods) are the most sensitive to pyrethroids

Distribution of LC50s among species, by taxonomic group

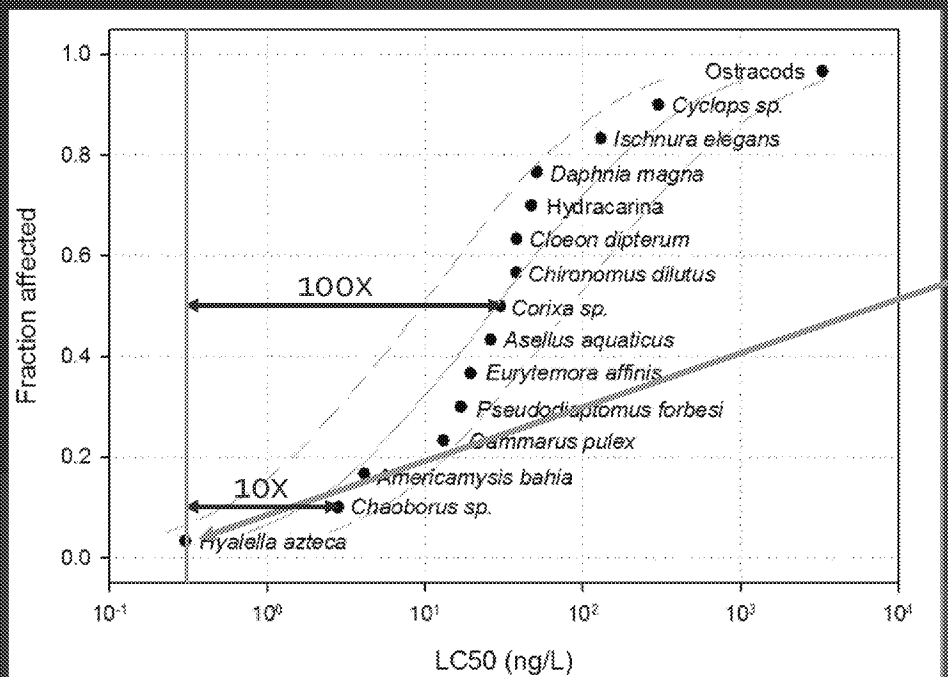


- Fish are 1000-fold less sensitive than *H. azteca*
- Mollusks and amphibians are 10,000-fold less sensitive than *H. azteca*

- Sensitivity of each species is expressed relative to *Hyalella azteca* for same AI
- Boxes show 25th, 50th, 75th percentiles; whiskers show 5th and 95th percentiles of species in each taxon

Example of an SSD

Lambda-cyhalothrin acute toxicity (LC50)
to 15 taxa of aquatic arthropods



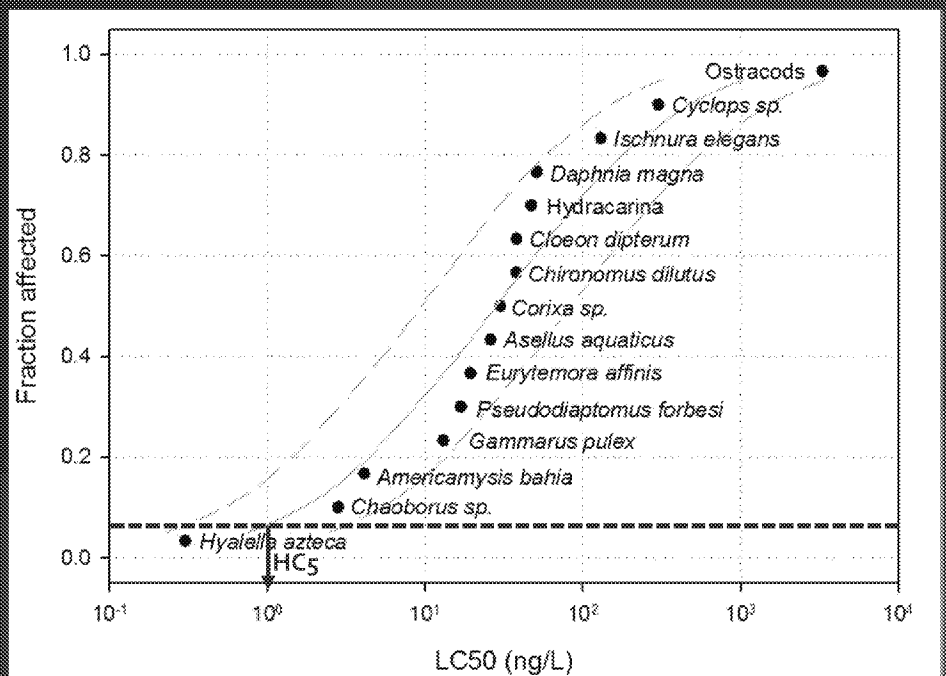
SSD modeled using EPA's SSD Generator

Most sensitive species (basis for screening level risk characterization)

- 10x more sensitive than the next most sensitive species
- 100x more sensitive than the median species

Example of an SSD

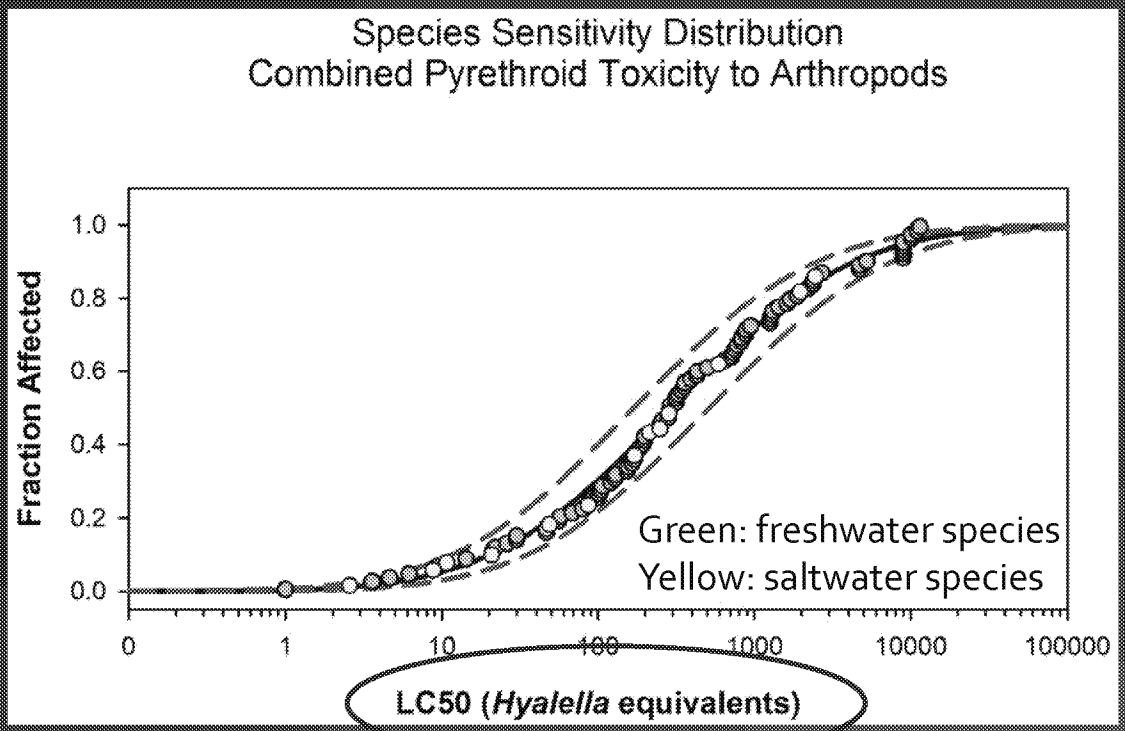
Lambda-cyhalothrin acute toxicity (LC_{50}) to 15 taxa of aquatic arthropods



SSD modeled using EPA's SSD Generator

- The 5th percentile of the SSD (HC_5) is a conservative measure of pyrethroid toxicity to sensitive species.
  - Widely used in environmental regulation, e.g. CWA
- Examples of interpretation
  - Fewer than 5% of species in an arthropod species assemblage would be affected at 1 ng/L.
  - There is less than 5% likelihood that the LC_{50} of (untested) Species X is below 1 ng/L.

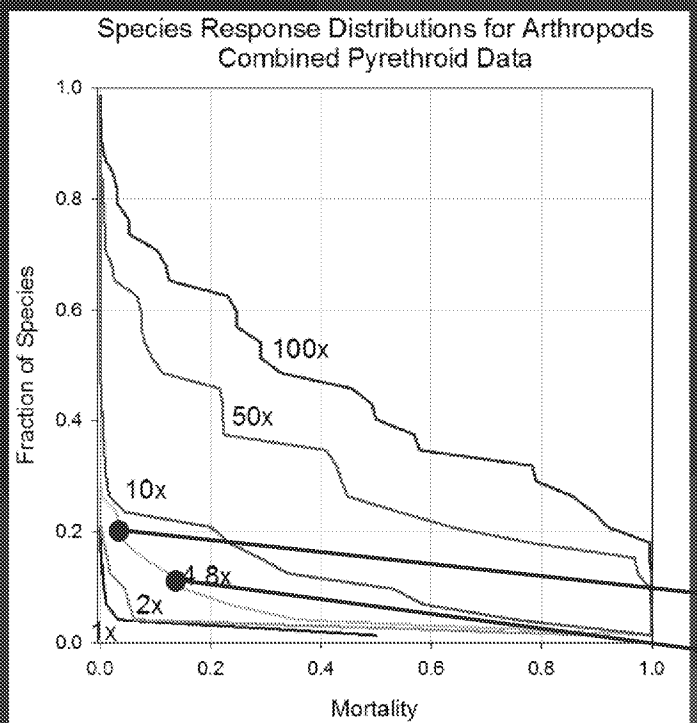
Combined pyrethroid SSD



SSD modeled using EPA's SSD Generator

- Because ecotox profiles are very similar across pyrethroids, data for multiple AIs can be combined into a single SSD.
- Large dataset confers statistical confidence.
- Large dataset expands ecological relevance.

Incorporating dose-response data: Species Response Distributions

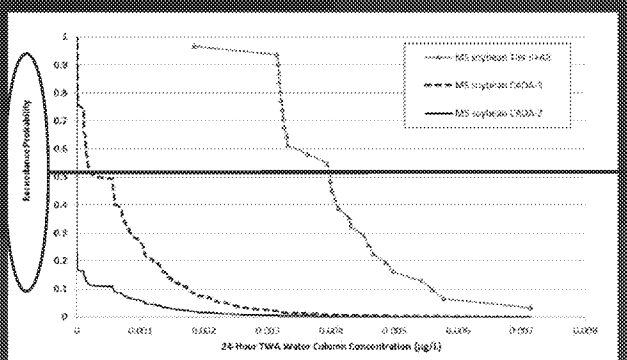


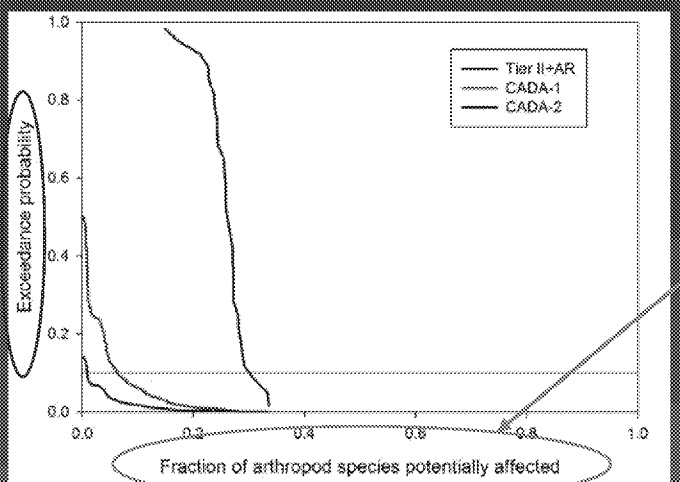
- Each curve shows the distribution of mortality rates (derived from dose-response curves) among species at a given concentration.
  - In this example, concentrations are expressed as multipliers of *Hyalella azteca* LC_{50}.
- At 4.8x (the HC_5 for the combined pyrethroid SSD):
  - < 3% mortality for 80% of species
  - < 15% mortality for 90% of species

Combining SSDs with exposure distributions (Joint Probability Curves)

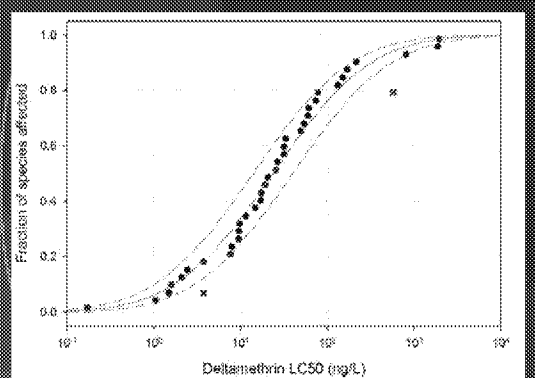
The SSD can be integrated with an EEC distribution to depict the relationship between the magnitude of effect (fraction of species affected) and the probability of its occurrence: a Joint Probability Curve (JPC).

EEC distribution



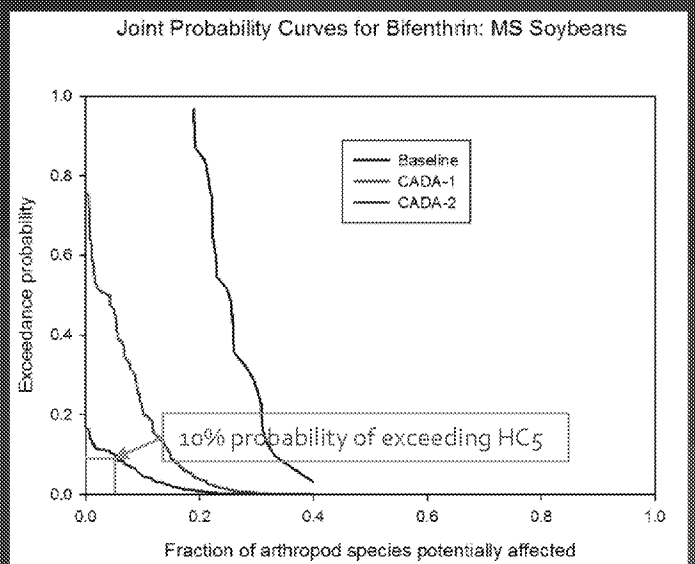


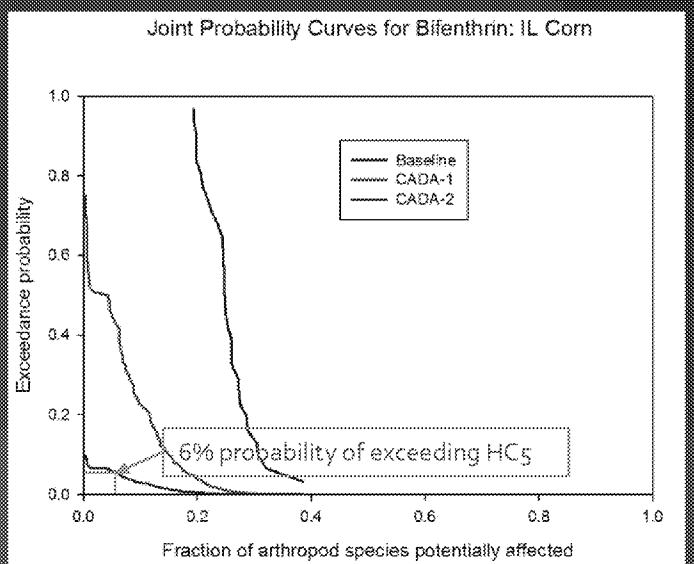
SSD



Joint Probability Curves

- These examples shows JPCs for screening level (baseline) and refined (CADA) exposure modeling.
- Based on refined exposure modeling, JPCs show that only a small fraction of species are likely to be affected by pyrethroid exposure.





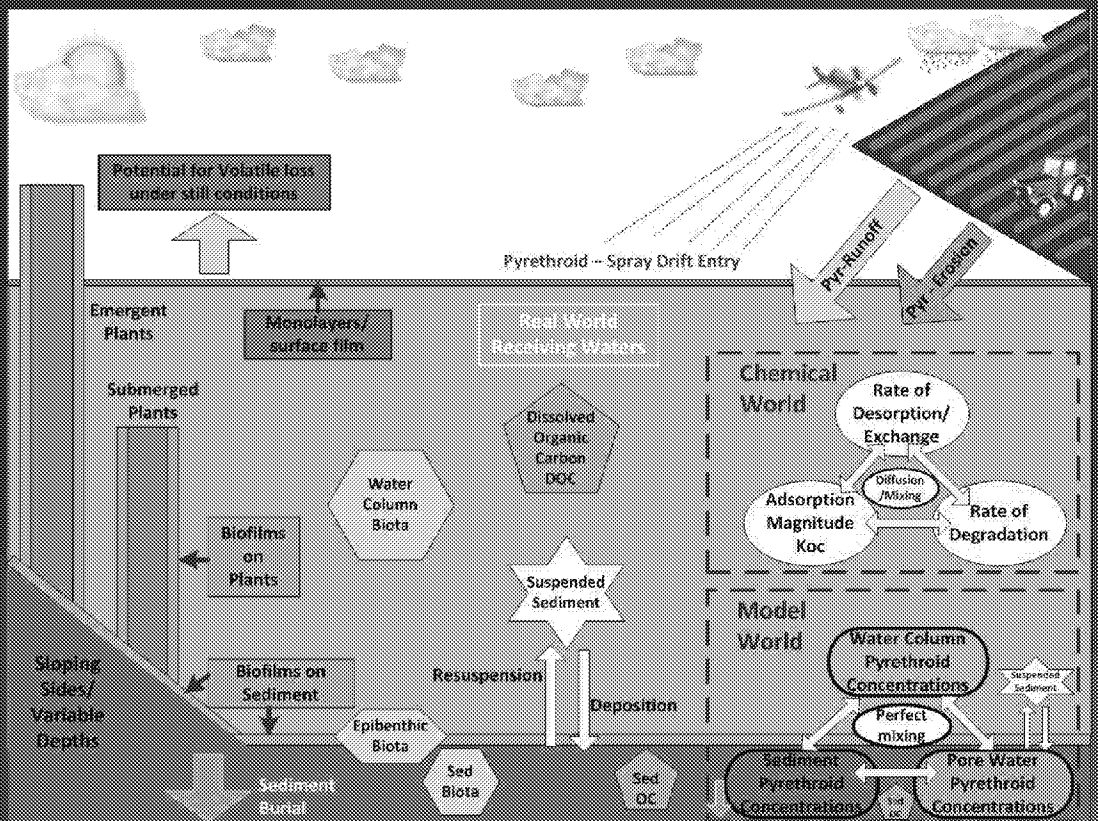
How can SSDs be incorporated into pesticide registration decisions?

- This information seems highly relevant to an understanding of the potential effects of a pesticide. How can such an analysis inform risk management decisions?
- The challenges to using SSDs are conceptual…
  - Need to refine risk question in terms of magnitude and probability of effects on individual species and on species assemblages
- …and institutional.
  - Lack of guidelines (although SSD methods are well documented)
  - Lack of higher tier regulatory standards (analogous to RQs and LOCs)

Higher-tier data used in PWG's risk assessment

- Species Sensitivity Distributions (SSDs)
- Refined exposure modeling
- Bioavailability calculations (using best-available K_{OC} values)
- Pathway ID study (runoff from outdoor residential uses)
- Landscape analysis
- Residue monitoring data
- Exposure uncertainty analysis
- Mesocosms
- Bioassessments

Refined exposure modeling



- Pyrethroids have unique characteristics – especially hydrophobicity – that are not properly represented by screening level models.

PWG modeling refinements

- Adapted a model (AGRO) that accounts for sediment dynamics; calibrated using pyrethroid field monitoring data
- Simulated effect of mandatory 10-foot vegetative filter strip (VFS) on runoff/erosion
- Improved drift estimates using RegDisp
- Adjusted application timing and method to match actual agronomic practice (maintaining maximum application rate and number)

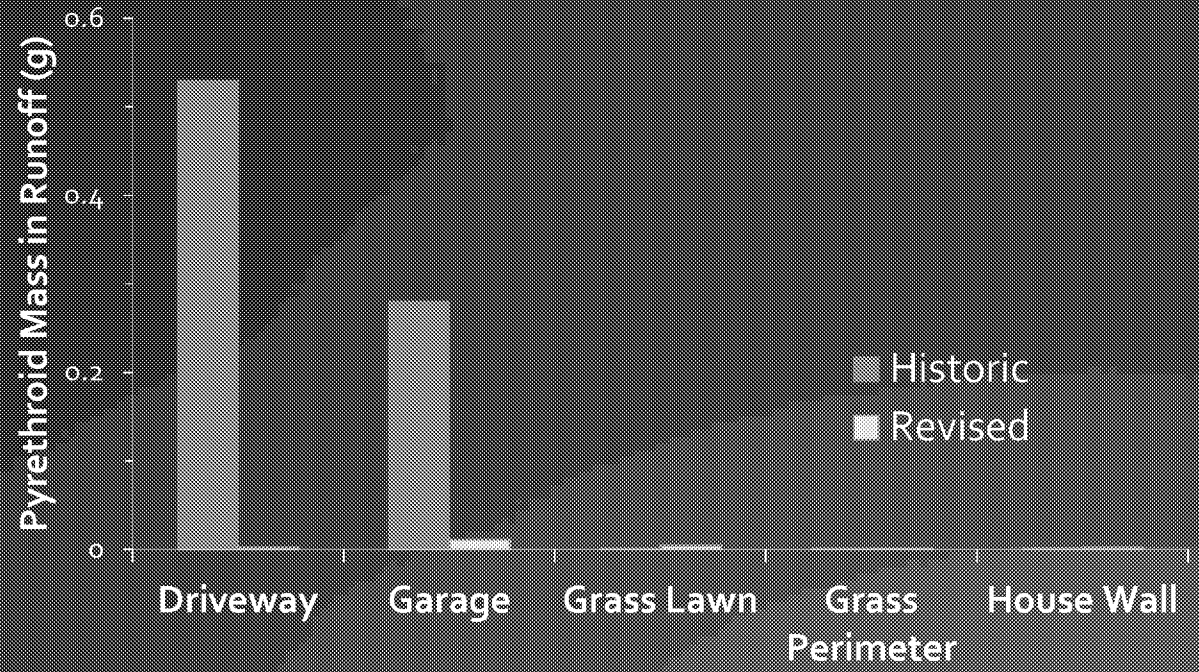
Partitioning and Bioavailability

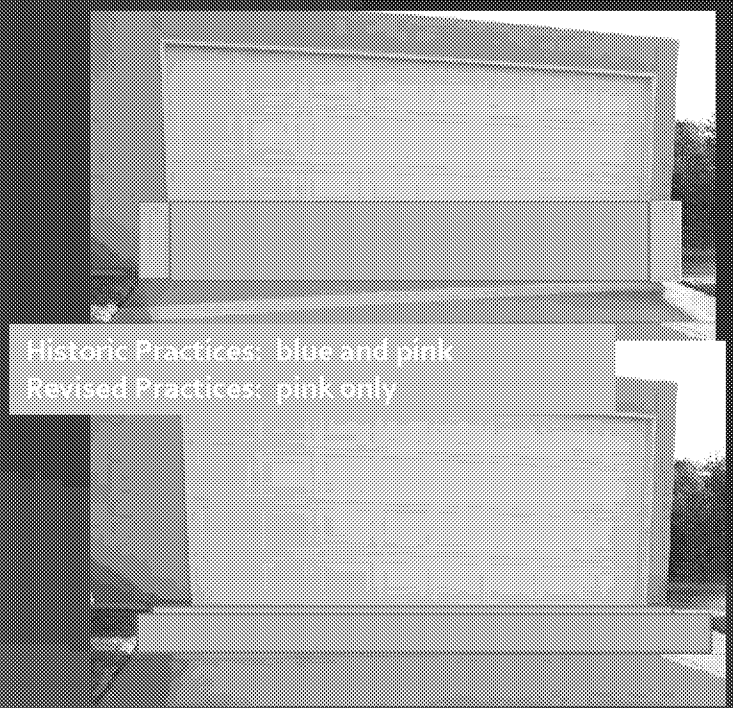
- Pyrethroids are extremely hydrophobic.
  - Accurate partition coefficients (K_{OC}, K_{DOC}) are needed for exposure modeling.
- Pyrethroid toxicity is mainly a function of freely dissolved concentrations.
  - Accurate partition coefficients are also needed for estimation of bioavailable (freely dissolved) pyrethroids in whole water samples.
- PWG developed K_{OC} and K_{DOC} values using solid-phase microextraction (SPME), which measures freely dissolved as well as total pyrethroid.
  - PWG's values have been adopted by some regulatory agencies.

Pathway ID Study

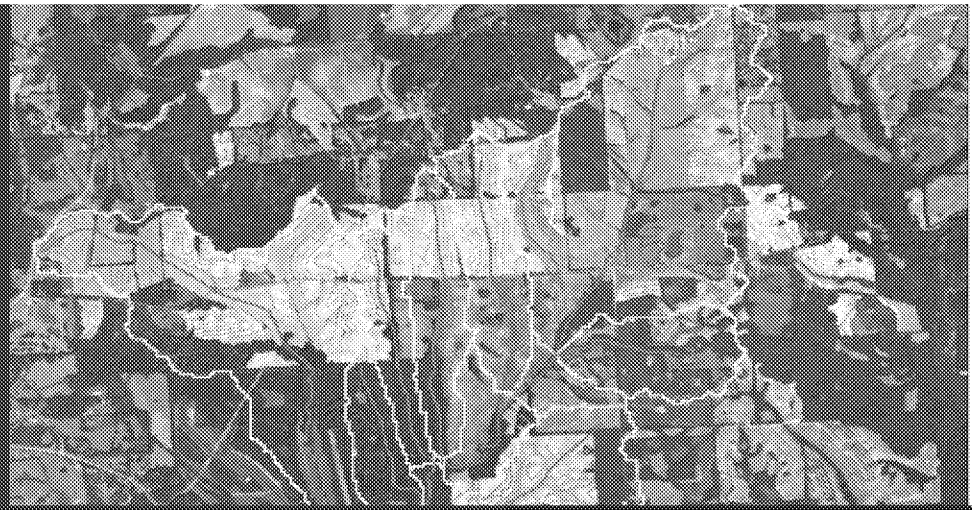
- Monitored off-target transport from multiple residential use patterns
- Determined residential use patterns driving off-site movement
  - Evaluated effectiveness of new label application restrictions
  - Essential to developing effective mitigation practices from all residential use patterns
- Compared historic practices vs. revised label
  - Treated house plots (front walls, front lawn, and driveway)
  - Residential lawn irrigation, natural & simulated rainfall
  - Study extended across several seasons

Pathway ID study confirmed that driveway, garage walls are key and that new label restrictions are effective





Landscape analysis

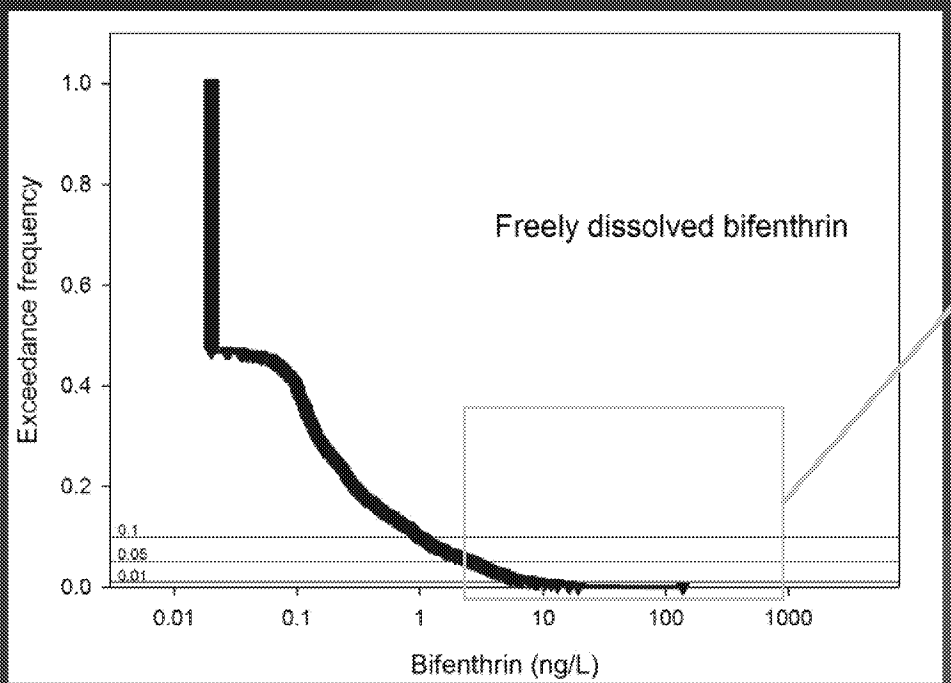


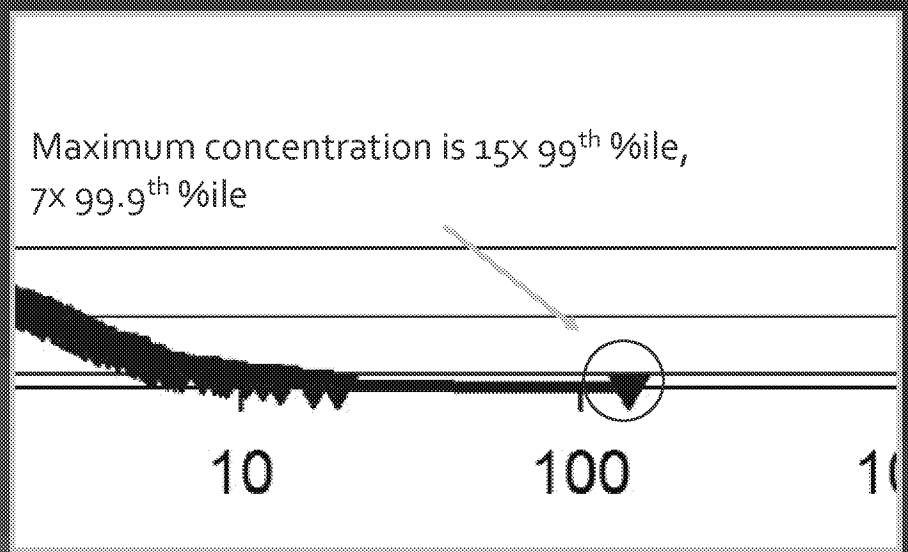
- Runoff/erosion potential at the catchment level
  - Comparing standard screening scenarios to real-world catchments
- Percent of catchment area treated with pyrethroid
- Proximity of use sites to water bodies

All of these have direct implications for exposure and risk.

Residue monitoring data

Freely dissolved bifenthrin concentrations in urban receiving waters (N=1418)

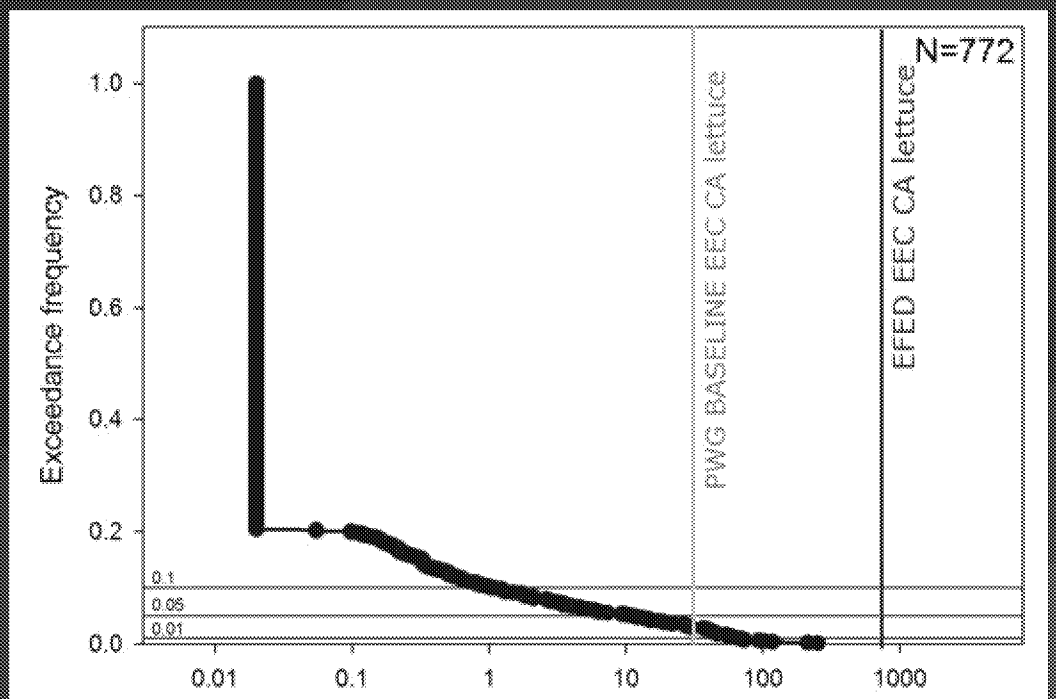




Maximum concentrations are not representative of the vast majority of samples in a large dataset

Screening-level EECs for agricultural scenarios are well above the range of freely dissolved concentrations in monitoring data.

Distribution of bifenthrin concentrations in water samples from agricultural sites



Screening-level EECs for agricultural scenarios are well above the range of freely dissolved concentrations in monitoring data.

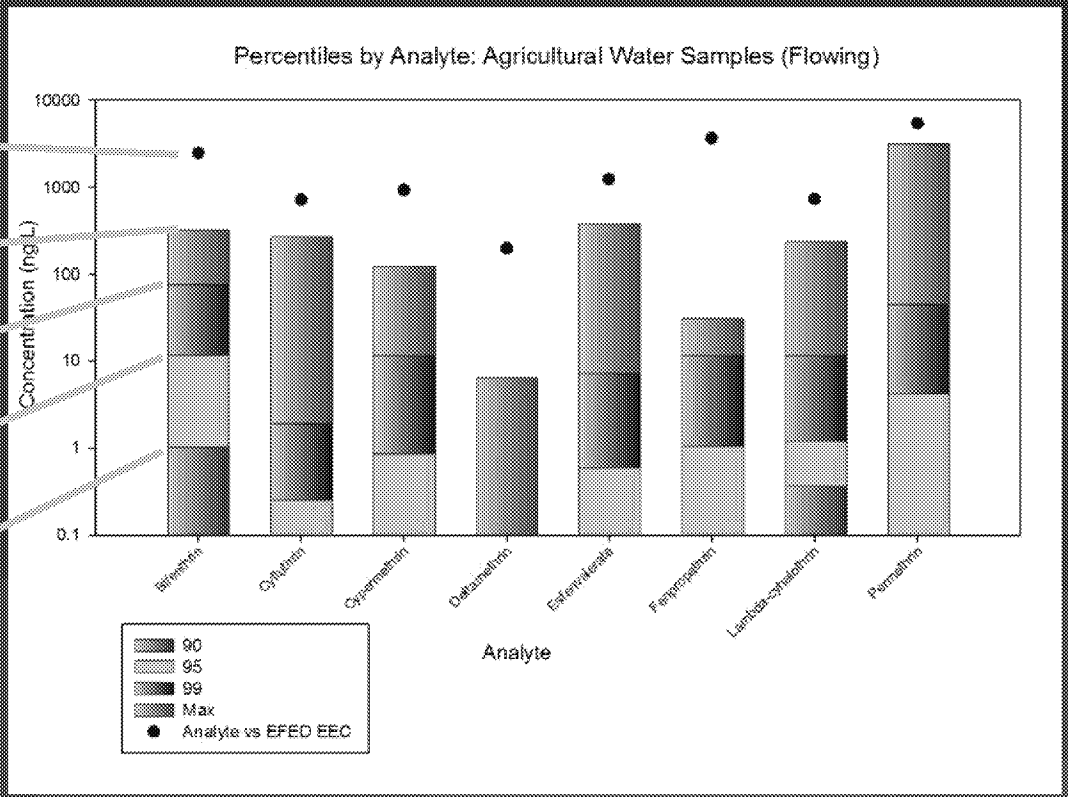
EEC

Max

99th %ile

95th %ile

90th %ile



Exposure uncertainty analysis

- The discrepancy between modeled and measured exposure concentrations led PWG to an exploration of model uncertainty.
- Exposure modeling deals with uncertainties and natural variability by making assumptions (explicit or implicit).
  - In the screening level, most assumptions are intentionally conservative.
- PWG identified over 30 key sources of uncertainty associated with exposure scenarios, model algorithms, and model input values.
- Tested the effect of uncertainties, individually and in combination, on model output (90th percentile EECs).

Implications of exposure uncertainty analysis

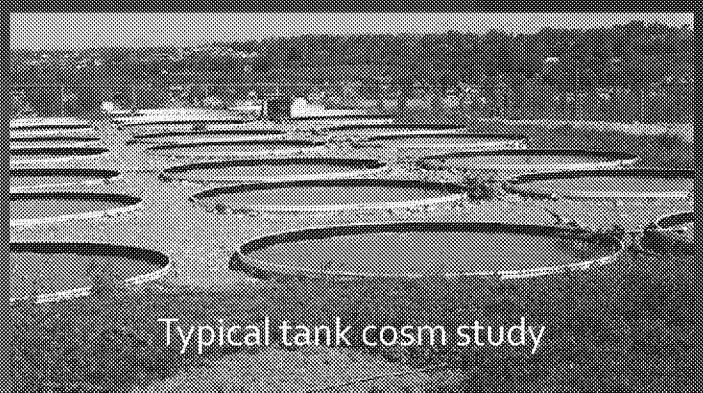
- When screening level model parameters were varied based on the likely range of real-world values, EECs were reduced.
  - Conservative estimates of the combined effect of uncertainties ranged from 5x to 380x across different crop scenarios.
  - If model was adjusted for Percent Cropped Area, ranged from 11x to nearly 10,000x.
- Nearly all of the LOC exceedances noted in the screening level assessment were eliminated when even a small subset of these uncertainties were considered.

Data from mesocosm studies

- More than 50 mesocosm studies with pyrethroids show that effects of realistic exposure levels on community structure and productivity are minimal.

Dutch ditch cosms

Typical FIFRA cosm study



Typical tank cosm study

Data from Bioassessments

Bioassessments evaluate the relationships between benthic community metrics and potential stressors such as physical habitat, metals, and pyrethroid concentrations.

- Benthic metrics
  - Taxonomic richness
  - Shannon diversity
  - % dominant taxon
  - Ephemeroptera taxa
  - EPT taxa
  - % tolerant taxa
  - % collectors/filterers
  - % collectors/gatherers
  - % grazers
  - % predators
  - % shredders
  - Abundance
- Data are analyzed using univariate and stepwise multiple regression techniques to identify stressors that have the greatest influence on the condition of benthic communities.

PWG's bioassessment data indicate that benthic communities are not being impacted by pyrethroids in California streams.

Key points

- Screening level assessments are useful as a starting point, but inferences (and regulatory decisions) can be made with greater accuracy and certainty if higher tier data are taken into account.
- Risk assessment hypotheses may need to be refined – and made more specific – before higher tier data can be incorporated.
- Different approaches to risk characterization are needed for higher tier assessment than for screening level assessment.
- Regulatory guidance is needed for generation of higher tier data and its use in risk assessment.

2017 Workshop on Innovation and Regulation in Agriculture

October 23-24, 2017

Organizers:

Linda Abbott, USDA
Danesha Seth Carley, NC State
George Cobb, Baylor University
Kevin Costello, US EPA
Jeff Giddings, Compliance Services International
Matt Kern, Waterborne Environmental
Ed Odenkirchen, US EPA
Laura McConnell, Bayer

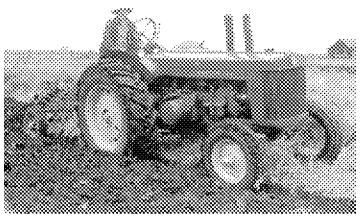
NC STATE UNIVERSITY

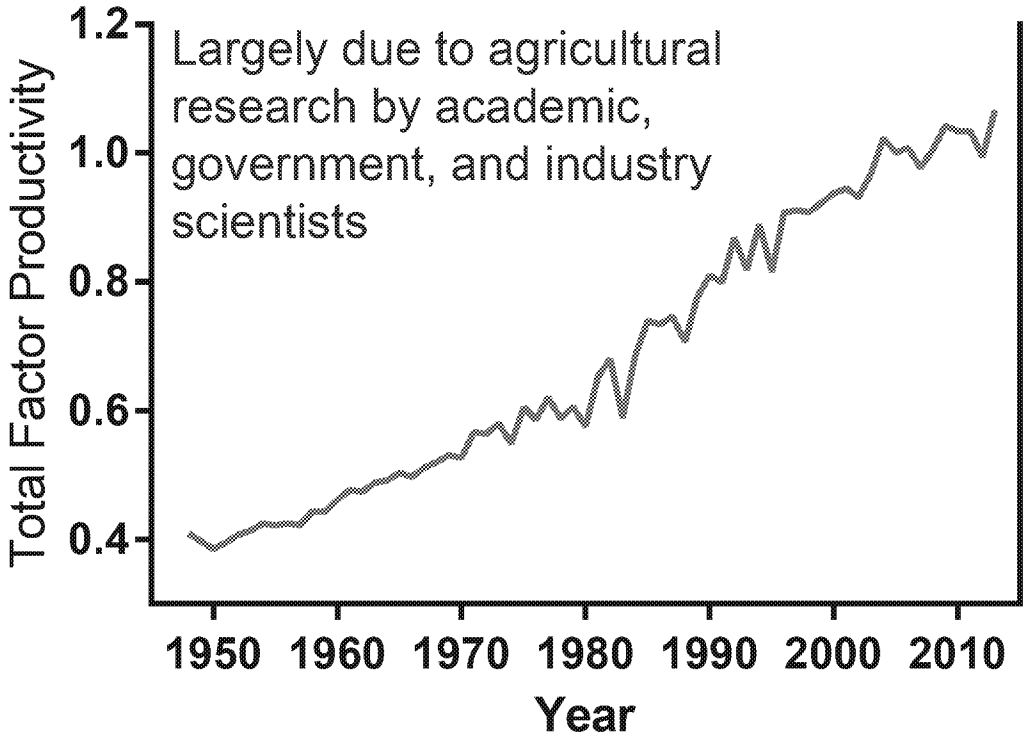
SETAC

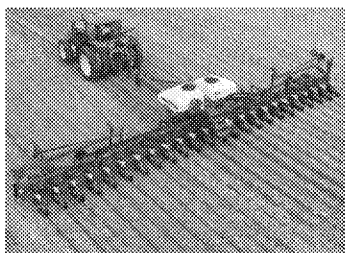
BAYER

North Carolina Biotechnology Center

For 70 years, US farm productivity has increased



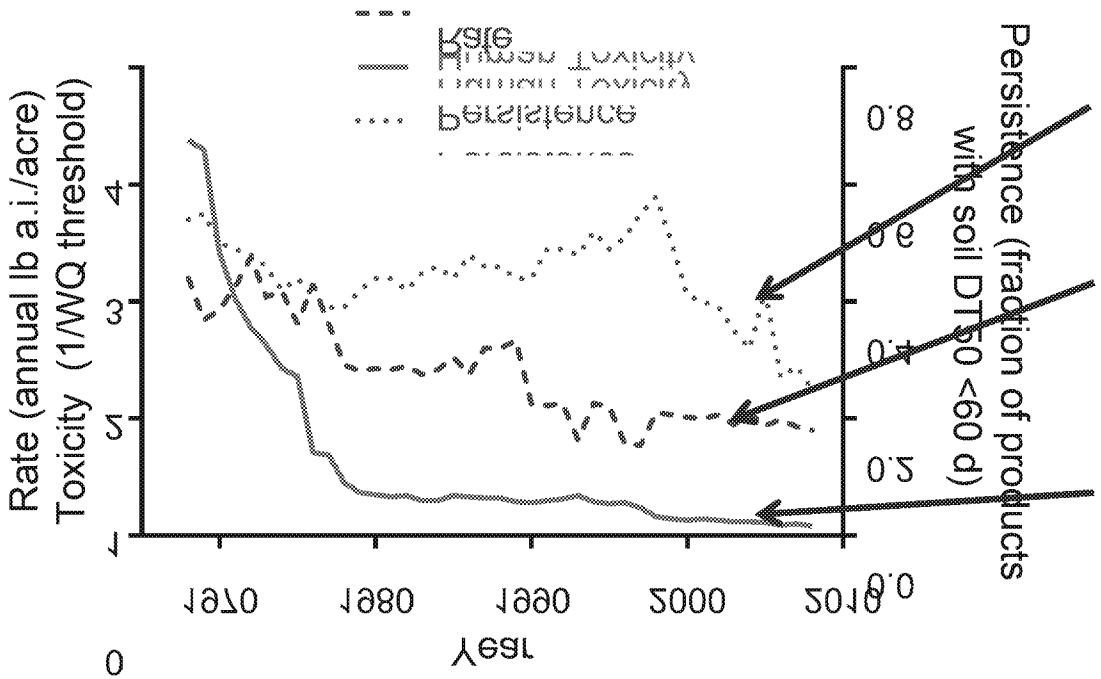




Agricultural Productivity Growth in the U.S. U.S. Department of Agriculture, Economic Research Service, http://www.ers.usda.gov/data-products/agricultural-productivity-in-the-us.aspx.

Quality of pesticides has improved over time

Achieved through innovation in the public and private sectors combined with extension programs, IPM and risk-based regulatory science approach.



J. Fernandez-Cornejo, R. Nehring, C. Osteen, S. J. Wechsler, A. Martin and A. Vialou *Pesticide Use in U.S. Agriculture: 21 Selected Crops, 1960-2008 Economic Information Bulletin No. (EIB-124)*, U.S. Department of Agriculture, Economic Research Service, Washington, DC, 2014.

The pace of technological innovation in agriculture has accelerated

NC STATE UNIVERSITY

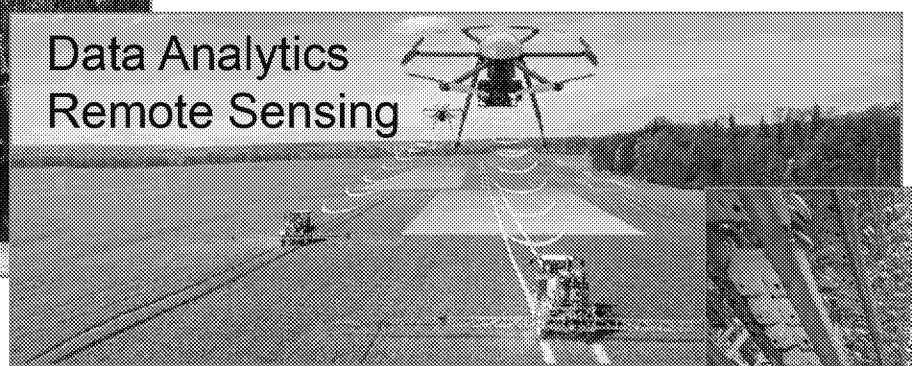
SETAC

BAYER

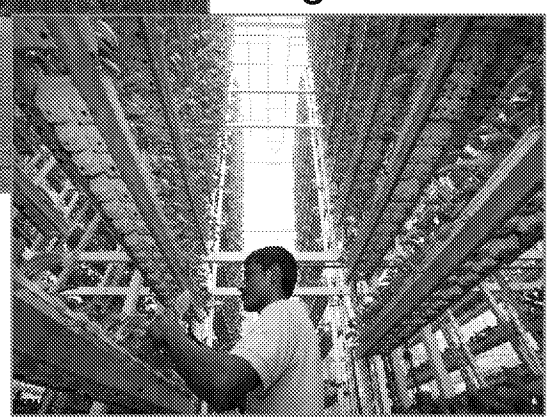
North Carolina Biotechnology Center

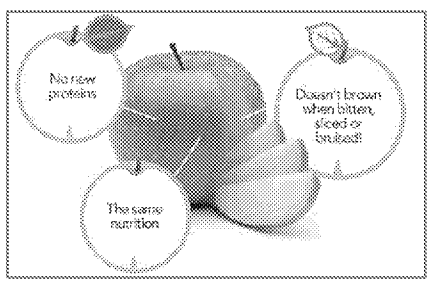
Automation

Data Analytics
Remote Sensing



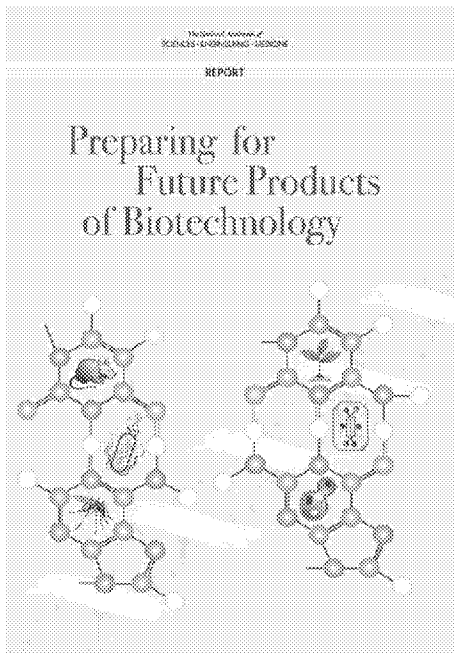
Urban agriculture





Plant Biotechnology

Research in regulatory science is needed now to prepare for the future of agriculture

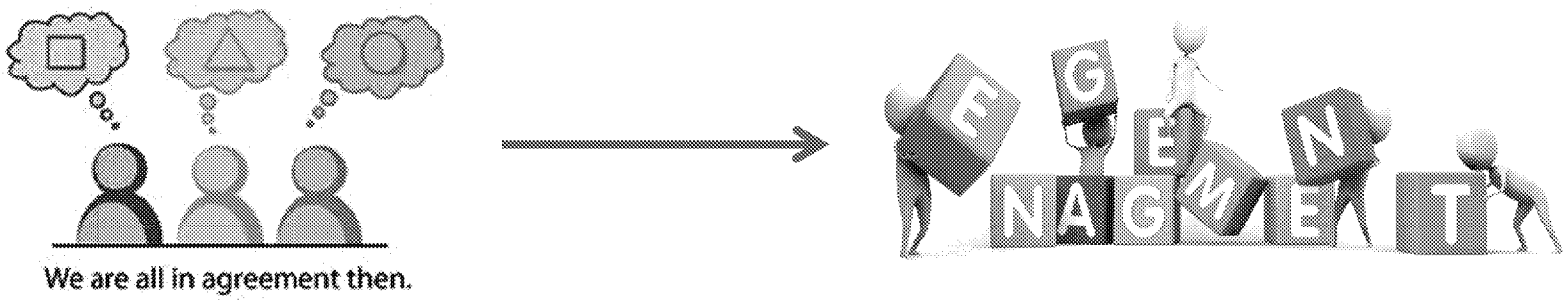


NAS, 2017. doi: https://doi.org/10.17226/24605

NAS Project Recommendations:

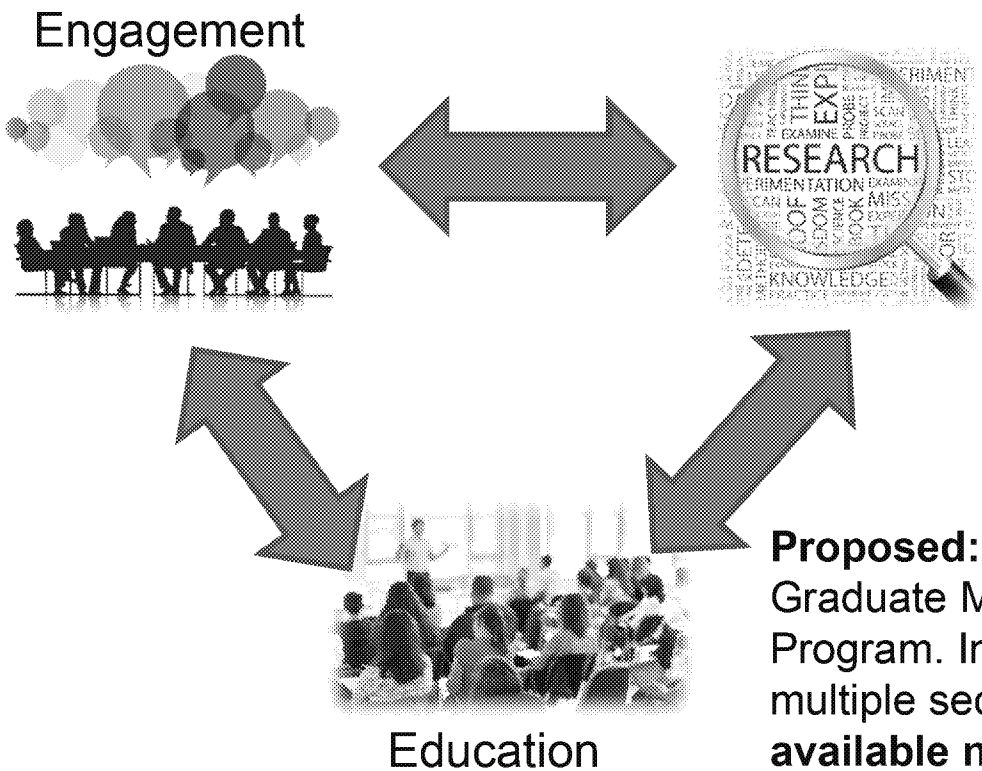
- *"Increased investments in **regulatory science will be needed**"*
- *"developers of biotechnology to **incorporate regulatory perspectives earlier in the product and technology development process***
- ***"appropriate federal funding levels** for sustained, multiyear research to develop the necessary **advances in regulatory science**."*

An effective **forum** for **engagement** is needed to advance regulatory science in agriculture



NC State Center for Regulatory Science in Agriculture

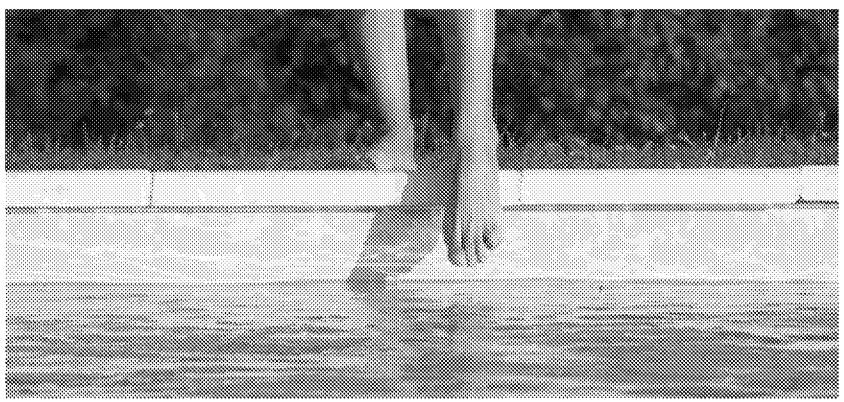
Proposed:
Forum for bringing together stakeholders including growers, engaging on emerging issues in regulatory science



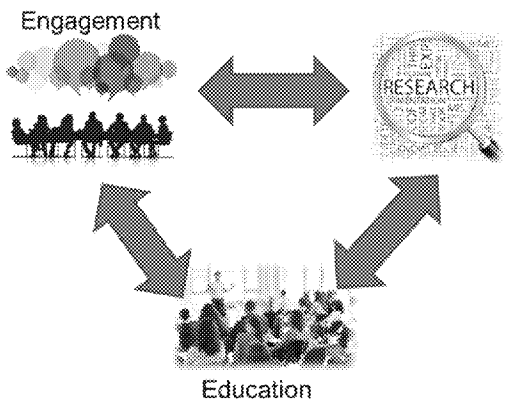
Proposed: Research to address issues emerging from engagement activities, involving scientists from multiple sectors

Proposed: Undergraduate Minor, Graduate Minor and Certificate Program. Include lecturers from multiple sectors. **Two courses available now**.

Today's workshop is where we begin to test the waters on engagement



Test the CRSA concept by engaging on an issue relevance to regulatory science in agriculture



This workshop is a test case or the first project of the proposed new Center

Utilize **pyrethroid insecticides**, as a case study for discussion. Currently under registration review by the US EPA.

- **Identify the greatest challenges** to the use of higher tier studies in ecological risk assessments and in risk management decisions.
- **Develop a series of recommendations** to improve the process for designing and conducting, evaluating and utilizing higher tier studies for risk assessment and risk management of pesticides.

Agenda

8:30 **Value of Pyrethroids in US Agriculture**
—Paul Mitchell, University of Wisconsin Madison

8:55 **Overview of US EPA Risk Assessment and Risk Management Approach to the Utilization of Higher Tier Studies**
—Kevin Costello and Ed Odenkirchen, US EPA Office of Pesticide Programs

9:20 Break

9:30 **Pyrethroid Risk Assessment, Consideration of Higher Tier Studies**
—Jeff Giddings, Compliance Services International

9:55 **Using a Weight of Evidence Approach in Ecological Risk Assessment**
—Keith Solomon, University of Guelph

10:20 **Discussion and Questions for Speakers**

11:00 End of Public Session

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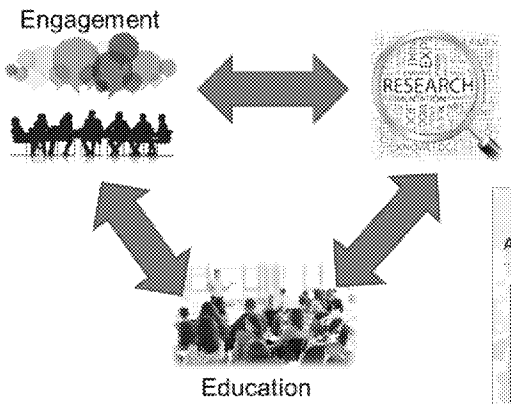
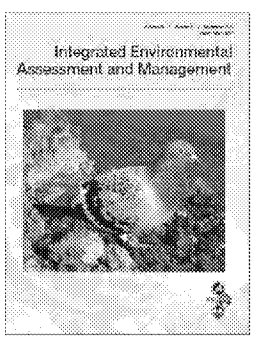
North Carolina Biotechnology Center

Test the CRSA concept by engaging on an issue relevance to regulatory science in agriculture





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Message

From: John Cummings [John.Cummings@fmc.com]
Sent: 5/31/2017 8:02:05 PM
To: Keigwin, Richard [Keigwin.Richard@epa.gov]
Subject: RE: A Few Discussion Topics

Thanks Rick. My suggestion is we talk by phone at 8AM on Tuesday. Hope that works.

John

John Cummings
North America Registration and Regulatory Affairs Manager | FMC Corporation
2929 Walnut Street | Philadelphia, PA 19104
work 215-299-6532 | cell 484-832-1452

From: Keigwin, Richard [mailto:Keigwin.Richard@epa.gov]
Sent: Wednesday, May 31, 2017 3:58 PM
To: John Cummings
Subject: Re: A Few Discussion Topics

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Rick Keigwin
Acting Director, Office of Pesticide Programs
U.S. Environmental Protection Agency

Sent from my iPhone

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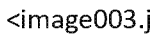

Message

From: Keigwin, Richard [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=151BAABB6A2246A3A312F12A706C0A05-RICHARD P KEIGWIN JR]
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8am Tuesday it is!

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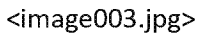

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> work 215-299-6532 | cell 484-832-1452
>
> <image002.jpg>
>
> ---
>
> **From:** Keigwin, Richard [mailto:Keigwin.Richard@epa.gov]
> **Sent:** Wednesday, May 31, 2017 3:02 PM
> **To:** John Cummings
> **Subject:** RE: A Few Discussion Topics
>
> I have some time on Tuesday at either 8am or 5pm. Would one of those times work for you?
>
> ---
>
> **From:** John Cummings [mailto:John.Cummings@fmc.com]
> **Sent:** Wednesday, May 31, 2017 11:59 AM
> **To:** Keigwin, Richard <Keigwin.Richard@epa.gov>
> **Subject:** RE: A Few Discussion Topics
>
> Thanks for the quick response Rick. FMC has a couple folks at the meeting so I avoided the travel. ☺
>
> Would you have any time on your calendar on Tuesday to meet in person? I am likely going to be down in DC anyway and it may be a better discussion in person. If so, then I may ask Jill Holihan to join us for the pyrethroid discussion as she is our non-Ag regulatory lead and is very familiar with the details.
>
> If you do not have time to meet in person we can certainly catch up by phone on Monday or Tuesday.

Safe travels.

John

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<image003.jpg>

From: Keigwin, Richard [mailto:Keigwin.Richard@epa.gov]
Sent: Wednesday, May 31, 2017 2:09 PM
To: John Cummings
Subject: RE: A Few Discussion Topics

John—

Good to hear from you. I'm in San Francisco at the MRL Workshop. Shouldn't you be here?

I fly back to DC tomorrow (Thursday) and won't be in the office on Friday.

Can we chat on Monday?

--Rick

From: John Cummings [mailto:John.Cummings@fmc.com]
Sent: Wednesday, May 31, 2017 10:32 AM
To: Keigwin, Richard <Keigwin.Richard@epa.gov>
Subject: A Few Discussion Topics

Hi Rick. I am hoping you have a few minutes to talk tomorrow or Friday regarding a few topics. Two of them are dimethoate/malathion PBPK and the pyrethroid preliminary ecological risk assessments. I am tied up the rest of today but am fairly open tomorrow until about 2PM. Friday is fairly open as well.

Thanks

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<image003.jpg>

Message

From: Keigwin, Richard [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=151BAABB6A2246A3A312F12A706C0A05-RICHARD P KEIGWIN JR]
Sent: 5/31/2017 7:01:47 PM
To: John Cummings [John.Cummings@fmc.com]
Subject: RE: A Few Discussion Topics

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Message

From: Keigwin, Richard [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=151BAABB6A2246A3A312F12A706C0A05-RICHARD P KEIGWIN JR]
Sent: 5/31/2017 6:09:24 PM
To: John Cummings [John.Cummings@fmc.com]
Subject: RE: A Few Discussion Topics

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